

## SPECIFICATION

### CYCLIC COMPOUNDS

#### TECHNICAL FIELD

The present invention relates to a novel cyclic compound exhibiting a cGMP specific phosphodiesterase (PDE) inhibitory activity (PDE V inhibitory activity) and being useful as a medicament, and a process for preparing the same.

#### BACKGROUND ART

In general, it is known that cGMP, which is an intracellular second messenger, is decomposed and inactivated by phosphodiesterase which is widely distributed in tissues of the living body, and when said PDE activity is inactivated, the level of cGMP in cells is increased, and as a result, various pharmacological activities, for example, relaxation of vascular smooth muscle, relaxation of bronchial smooth muscle, and inhibition of platelet aggregation are exhibited.

Moreover, it has been reported that such cGMP specific PDE inhibitors (i.e., PDE V inhibitors) are useful in the treatment of diseases caused by a functional disorder of cGMP-signaling, including hypertension, angina pectoris, myocardial infarction, chronic or acute heart failure, pulmonary hypertension, etc. (cf., PCT Patent Publication WO 96/05176, etc.), and prostatic hyperplasia (Australian Patent Publication No. 9955977). It has also been reported that PDE V inhibitors may be useful in the treatment of female sexual dysfunction (Vemulapalli et al., Life Sciences, 67, 23-29 (2000)), diabetic gastroparesis (Watkins et al., J. Clin. Invest. 106: 373-384 (2000)), achalasia (Bortolotti et al., Gastroenterology; 118: 253-257 (2000)), diarrhea (Mule et al., Br. J. Pharmacol., 127, 514-20 (1999)), constipation (Bakre et al., J. Cell. Biochem. 77: 159-167 (2000)) and asthma (Turner et al., Br. J. Pharmacol., 111, 1198-1204 (1994)).

Furthermore, it has been also reported that 1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-phenylsulfonyl]-4-methylpiperazine [general name: Sildenafil] having PDE V inhibitory activity is useful in the treatment of diseases such as penile erectile dysfunction (copulative impotence), etc. (cf., Boolell et al., The Journal of Urology, Supplement, vol. 155, no. 5, p. 495A739 (1996); Terrett et al., Bioorganic & Medicinal Chemistry Letters, vol. 6, no. 15, p. 1819 (1996); and Ballard et al., British Journal of Pharmacology, Proceeding Supplement, vol. 118, p. 153 (1996)).

However, sildenafil has been reported to have side effects such as headache, facial suffusion, gut disorder, rhinitis, color sense disorder, penile erectile continuance, etc. (Irwin et al., The New England Journal of Medicine, vol. 338, no. 20, p. 1397-1404 (1998); Morales et al., International Journal of Impotence Research, vol. 10, no. 2, p. 69-73 (1998); and Goldenberg, Clinical Therapeutics, vol. 20, no. 6, p. 1033-1048 (1998)).

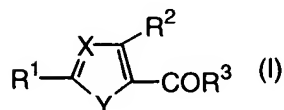
In addition, sildenafil has also been reported that the effects of sildenafil on light response of retina tissues and its PDE VI inhibitory activity correlate each other in the experiments on dogs (Morales et al., International Journal of Impotence Research, vol. 10, no. 2, p. 69-73 (1998)), while it has been reported that PDE VI on retina plays an importance role in the sensation of light (Morrales et al., International Journal of Impotence Research, vol. 10, no. 2, p. 69-73 (1998); Estrade et al., European Journal of Pharmacology, vol. 352, p. 157-163 (1998)).

#### DISCLOSURE OF INVENTION

An object of the present invention is to provide a novel cyclic compound showing an excellent phosphodiesterase V (PDE V) inhibitory activity, and being useful as a remedy for the prophylaxis or treatment of penile erectile dysfunction with few side

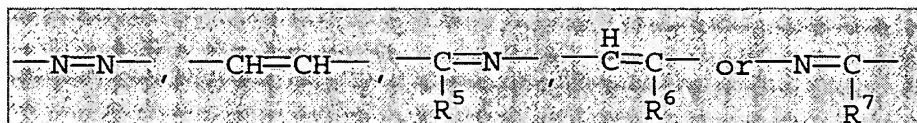
effects. Another object of the present invention is to provide a process for preparing such a cyclic compound.

The present invention is to provide a cyclic compound of the formula (I) or a pharmacologically acceptable salt thereof,



wherein X is =CH— or =N—,

Y is —NH—, —NR<sup>4</sup>—, —S—, —O—, —CH=N—, or —N=CH—,



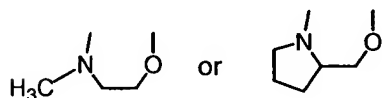
R<sup>1</sup> is a lower alkoxy group which is optionally substituted, an amino group which is optionally substituted, a heterocyclic ring containing N atom(s) which is optionally substituted, a hydroxy group which is optionally substituted by a heterocyclic ring containing N atom(s) which is optionally substituted, or cyano group,

R<sup>2</sup> is a lower alkylamino group which is optionally substituted by an aryl group which is optionally substituted, a lower alkoxy group which is optionally substituted by an aryl group which is optionally substituted, a lower alkoxy group substituted by an aromatic heterocyclic ring containing N atom(s), a lower alkylamino group substituted by a heterocyclic ring which is optionally substituted, or an amino group substituted by an aryl group which is optionally substituted,

R<sup>3</sup> is an aryl group which is optionally substituted, a heterocyclic ring containing N atom(s) which is optionally substituted, a lower alkyl group which is optionally substituted, a lower alkoxy group which is optionally substituted, a cyclo lower alkoxy group which is optionally substituted, a hydroxy group substituted by a heterocyclic ring

containing N atom(s) which is optionally substituted, or an amino group which is optionally substituted, and

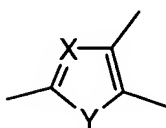
$R^4$ ,  $R^5$ ,  $R^6$  or  $R^7$  is an aryl group which is optionally substituted, a heterocyclic ring containing N atom(s) which is optionally substituted, a lower alkoxy group which is optionally substituted, or an amino group which is optionally substituted, and  $R^4$ ,  $R^5$ ,  $R^6$  or  $R^7$  may combine with  $R^3$  to form a lactone ring represented by the following formula,



wherein, when X is =N-, Y is -CH=N-, or -N=CH-,  $R^2$  is an amino group mono-substituted by a methyl group substituted by an aryl which is optionally substituted, and  $R^3$  is a lower alkyl which is optionally substituted, an amino group mono-substituted by a lower alkyl group substituted by a heterocyclic ring containing N atom(s) which is optionally substituted, an amino group mono-substituted by a heterocyclic ring containing N atom(s) which is optionally substituted or an amino group mono-substituted by a cyclo lower alkyl group which is optionally substituted,  $R^1$  is a lower alkoxy group which is optionally substituted, an amino group which is optionally substituted, a hydroxy group which is optionally substituted by a heterocyclic ring containing N atom(s) which is optionally substituted, or cyano group.

#### THE BEST MODE FOR CARRYING OUT THE INVENTION

As a ring represented by the following formula in the compound (I),



wherein X and Y are the same as defined above,

is illustrated benzene ring or a 5-6 membered monocyclic hetero ring containing N atom(s), such as phenyl group, or a 5-6 membered aromatic monocyclic hetero ring (e.g.



pyrrolyl, thienyl, furyl, imidazolyl, thiazolyl, oxazolyl, pyridyl, pyrimidinyl, pyridazinyl, 1,2,4-triazinyl).

As "a lower alkoxy group which is optionally substituted", represented by  $R^1$ , is illustrated a lower alkoxy group which is optionally substituted by one to three, same or different substituents selected from the group consisting of an cyclo lower alkyl group, hydroxy group, a lower alkylamino group which is optionally protected, a lower alkoxy group, a lower alkyl group substituted by hydroxy group, an aryl group, a lower alkoxyaryl group, a lower alkylaryl group substituted by hydroxy group, an aryl group substituted by halogen atom(s), furyl group, pyridyl group, a lower alkoxy pyridyl group, a lower alkylpyridyl group substituted by hydroxy group, a lower alkylpyridyl group, a pyrimidinyl group, a lower alkoxy pyrimidinyl group, and a morphorinyl group.

As "an amino group which is optionally substituted", represented by  $R^1$ , is illustrated a lower alkylamino group which is optionally substituted by one to three, same or different substituents selected from the group consisting of a hydroxy group, a lower alkoxy group, a pyridyl group, a lower alkylamino group, cyano group, phenyl group, a phenyl group which is optionally substituted by a lower alkoxy group and/or a halogen atom, an indanyl group and a lower alkyl group substituted by hydroxy group, or an indanylamino group.

As a heterocyclic ring containing N atom(s) of "a heterocyclic ring containing N atom(s) which is optionally substituted", represented by  $R^1$ , is illustrated a 5-14 membered mono- or bi-cyclic hetero ring containing N atom(s), more concretely a 5-6 membered monocyclic hetero ring containing N atom(s), or a 8-12 membered bicyclic hetero ring containing N atom(s), furthermore concretely, a 5-6 membered non-aromatic monocyclic hetero ring containing N atom(s), such as a pyrrolidinyl group, a piperazinyl group, a piperidyl group, or a 8-10 membered bicyclic hetero ring containing N atom(s)

formed by fusing above mentioned mono- 5-6 membered non-aromatic hetero ring containing N atom(s) together with a mono- 5-6 membered aromatic ring containing N atom(s), such as 1H-2,3-dihydropyrrolo[3,4-b]pyridin-2-yl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl or 5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl. These heterocyclic rings containing N atom(s) are optionally substituted by one to four, same or different substituents selected from the group consisting of hydroxy group, an amino group which is optionally protected, a lower alkyl group, a lower alkoxy group, a lower alkoxy carbonyl group, a lower alkyl group substituted by hydroxy group, oxo group, a pyridyl group, a pyrimidinyl group, formyl group, mesyl, a lower alkanoyl group substituted by hydroxy group which is optionally protected, a lower alkoxy-substituted lower alkyl group, a carbamoyl group, a benzylamino group in which the benzene ring is substituted by a lower alkoxy group, and a benzylamino group in which the benzene ring is substituted by a halogen atom.

As "a hydroxy group which is optionally substituted by a heterocyclic ring which is optionally substituted", represented by  $R^1$ , is illustrated a hydroxy group which is optionally substituted by a hetero cyclic ring containing N atom(s) selected from the group consisting of a piperidyl group, a lower alkyl piperidyl group and a pyridyl group.

As an aryl group of "an aryl which is optionally substituted", represented by  $R^2$ , is illustrated a 5-10 membered mono- or bicyclic aromatic hydrocarbon ring, more concretely phenyl group or naphthyl group. As a substituent of "an aryl group which is optionally substituted", in case of "a lower alkylamino group which is optionally substituted by an aryl group which is optionally substituted", is one to four, same or different, groups selected from a lower alkoxy group, a halogen atom, an amino group which is optionally protected, hydroxy group, a lower alkoxy pyridyl group, a lower alkylamino group which is optionally protected, nitro group, a lower alkyl group

substituted by a halogen atom, a lower alkylendioxy group, cyano group, a lower alkyl group substituted by a hydroxy group which is optionally protected, a lower alkylsulfonyl group and a lower alkylsulfinyl group. In case of "a lower alkoxy group which is optionally substituted by an aryl group which is optionally substituted", said aryl group is optionally substituted by one to four, same or different, substituents selected from the group consisting of a lower alkoxy group, a halogen atom and cyano group.

As "a lower alkoxy group substituted by an aromatic heterocyclic ring containing N atom(s)", represented by  $R^2$ , is illustrated a lower alkoxy group substituted by one to three, same or different, aromatic heterocyclic rings containing N atom(s) selected from the group consisting of a pyridyl group, a pyrimidinyl group and a pyrazinyl group.

As "a lower alkylamino group substituted by a heterocyclic ring which is optionally substituted", represented by  $R^2$ , is illustrated a lower alkylamino group substituted by one to four, same or different, heterocyclic rings which are optionally substituted selected from the group consisting of an indolyl group, a pyrimidinyl group, a benzofuranyl group, a dihydrobenzofuranyl group, a lower alkylpyrimidinyl group, a dihydrobenzoxazolyl group and a dihydrobenzoimidazolyl group.

As "an aryl group which is optionally substituted", represented by  $R^3$ , is illustrated an aryl group which is optionally substituted by one to four, same or different, substituents selected from a lower alkoxy group and a lower alkylamino group, or an aryl group which is optionally substituted by one or two lower alkylendioxy groups. As "an aryl group", is illustrated a 5-10 membered mono- or bicyclic aromatic hydrocarbon, such as phenyl group or naphthyl group.

As a heterocyclic ring containing N atom(s) of "a heterocyclic ring containing N atom(s) which is optionally substituted", represented by  $R^3$ , is illustrated a 5-6 membered monocyclic hetero ring containing N atom(s), such as a 5-6 membered non-

aromatic monocyclic hetero ring containing N atom(s), e.g. a piperidyl group, a piperazinyl group, or a morpholinyl group, or such as a 5-6 membered aromatic monocyclic hetero ring containing N atom(s), e.g. a pyrimidinyl group, a pyridazinyl group, a pyridyl group or an imidazolyl group. Said heterocyclic ring containing N atom(s) is optionally substituted by one to four, same or different, substituents selected from the group consisting of a lower alkyl group, hydroxy group, an amino group, chlorosulfinyloxy group and piperidinylloxysulfinyloxy group.

As "a lower alkyl group which is optionally substituted", represented by  $R^3$ , is illustrated a lower alkyl group which is optionally substituted by one to three, same or different, substituents selected from the group consisting of a morpholinyl group, a pyridyl group, a lower alkylsulfonyl group and a di-lower alkoxyphosphoryl group.

As "a lower alkoxy group which is optionally substituted", represented by  $R^3$ , is illustrated a lower alkoxy group which is optionally substituted by one to three, same or different, substituents selected from the group consisting of a pyridyl group, a lower alkoxy pyridyl group, a pyrimidinyl group, a lower alkylamino group, a pyrazinyl group, a lower alkoxy group which is optionally substituted by a phenyl group, a pyrimidinyl-substituted oxy group, a pyridyl-substituted oxy group, a pyrimidinyl-substituted lower alkoxy group, a morpholinyl group, a lower alkylmorpholinyl group, a N-lower alkyl-N-pyrimidinylamino group, a di-lower alkyl dioxolanyl group, a lower alkoxy lower alkoxy group, a pyridylcarbonylamino group, hydroxy group, a piperidyl group and a lower alkylpiperidyl group.

As "a cyclo lower alkoxy group which is optionally substituted", represented by  $R^3$ , is illustrated a cyclo lower alkoxy group which is optionally substituted by hydroxy group.

As "a hydroxy group substituted by a heterocyclic ring containing N atom(s) which is optionally substituted", represented by  $R^3$ , is illustrated a hydroxy group

substituted by a heterocyclic ring containing N atom(s) which is optionally substituted by one to four, same or different, substituents selected from a pyrimidinyl group and cyano-substituted lower alkyl group.

As "an amino group which is optionally substituted", represented by  $R^3$ , is illustrated an amino group which is optionally substituted by one or two, same or different, substituents selected from the group consisting of (i) a lower alkoxy group which is optionally substituted by a lower alkoxy group, (ii) a lower alkyl group which is optionally substituted by one to three, same or different, substituents selected from the group consisting of cyano group, hydroxy group, a lower alkoxy group, a phenyl group which is optionally substituted by a lower alkoxy group and/or a halogen atom, carbamoyl group, a lower alkylamino group, a pyridyl group, a lower alkylpyridyl group, a lower alkoxy pyridyl group, a pyrimidinyl group, a lower alkoxypyrimidinyl group, a morpholinyl group, a lower alkylmorpholinyl group, a hydroxy-substituted lower alkylmorpholinyl group, a cyano-substituted lower alkylmorpholinyl group, a hydroxy-substituted piperidyl group, an oxo-substituted piperazinyl group, a lower alkylpiperazinyl group, a lower alkylsulfonylpiperazinyl group, a pyrrolidinyl group, a lower alkylpyrrolidinyl group, a lower alkylpiperazinyl group, a tetrahydrofuranyl group, a lower alkoxyphenoxy group, a lower alkoxy pyridylamino group and a pyrimidinylamino group, (iii) phenyl group which is optionally substituted by hydroxy group or a lower alkoxy group, (iv) a pyridyl group which is optionally substituted by a lower alkyl group, (v) a pyrimidinyl group, (vi) a pyrazolyl group which is optionally substituted by a lower alkyl group, (vii) an isoxazolyl group which is optionally substituted by a lower alkyl group, (viii) a benz[b]morpholinyl group which is optionally substituted by oxo group, (ix) a morpholinyl group, (x) a piperidyl group which is optionally substituted by one to four, same or different, substituents selected from the group consisting of a lower

alkoxycarbonyl group, a lower alkyl sulfonyl, a lower alkyl group, a cyano-substituted lower alkyl group, a hydroxy-substituted lower alkanoyl group, formyl group, a lower alkoxy-substituted lower alkanoyl group and a lower alkylamino-substituted lower alkanoyl group, (xi) a cyclo lower alkyl group which is optionally substituted by one to three, same or different, substituents selected from hydroxy group which is optionally protected, a lower alkoxy group and a pyrimidinyl-substituted oxy group, and (xii) a pyrimidinylamino group which is optionally substituted by a lower alkyl group and a lower alkoxycarbonyl group.

Further, as a protective group of an amino group, a lower alkylamino group and hydroxyl group, is illustrated formyl group, a lower alkanoyl group, etc.

In substituents represented by  $R^4$ ,  $R^5$ ,  $R^6$  or  $R^7$ ,  
as "an aryl group which is optionally substituted", is illustrated a phenyl group which is optionally substituted by a lower alkoxy group,  
as "a heterocyclic ring containing N atom(s) which is optionally substituted", is illustrated a heterocyclic ring containing N atom(s) which is optionally substituted by hydroxy group, a lower alkyl group or a hydroxy-substituted lower alkyl group,  
as "a heterocyclic ring containing N atom(s)", is illustrated a 5-14 membered monocyclic or bicyclic hetero ring, more concretely, a 5-6 membered monocyclic hetero ring containing N atom(s) or a 8-12 membered bicyclic hetero ring containing N atom(s), further more concretely, a 5-6 membered non-aromatic monocyclic hetero ring containing N atom(s), such as a pyrrolidinyl group, piperazinyl group, a piperidyl group, or a 8-10 membered bicyclic hetero ring containing N atom(s), which is a 5-6 membered aromatic monocyclic hetero ring containing N atom(s) fused to the above 5-6 membered non aromatic monocyclic hetero ring containing N atom(s), such as 1H-2,3-



hetero cyclic ring containing N atom(s) means a 5-14 membered mono- or bi-cyclic hetero ring containing N atom(s).

Preferrable compounds (I) of the present invention are compounds (I) wherein

X is =N-,

Y is —NH—, —NR<sup>4</sup>—, —S—, —O—, —CH=N—, —N=CH—, —N=

N—, —CH=CH—,  $\begin{array}{c} \text{—C=N—} \\ | \\ \text{R}^5 \end{array}$ ,  $\begin{array}{c} \text{H} \\ | \\ \text{—C=C—} \\ | \\ \text{R}^6 \end{array}$  or  $\begin{array}{c} \text{—N=C—} \\ | \\ \text{R}^7 \end{array}$ ,

R<sup>1</sup> is a lower alkoxy group which is optionally substituted, an amino group which is optionally substituted, a heterocyclic ring containing N atom(s) which is optionally substituted, a hydroxy group which is optionally substituted by a heterocyclic ring containing N atom(s) which is optionally substituted, or cyano group,

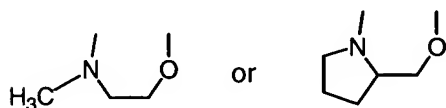
R<sup>2</sup> is a lower alkylamino group which is optionally substituted by an aryl group which is optionally substituted, a lower alkoxy group which is optionally substituted by an aryl group which is optionally substituted, a lower alkoxy group substituted by an aromatic heterocyclic ring containing N atom(s) which is optionally substituted, a lower alkylamino group substituted by a heterocyclic ring which is optionally substituted, or an amino group substituted by an aryl group which is optionally substituted,

R<sup>3</sup> is an aryl group which is optionally substituted, a heterocyclic ring containing N atom(s) which is optionally substituted, a lower alkyl group which is optionally substituted, a lower alkoxy group which is optionally substituted, a cyclo lower alkoxy group which is optionally substituted, a hydroxy group substituted by a heterocyclic ring containing N atom(s) which is optionally substituted, or an amino group which is optionally substituted, and

R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> or R<sup>7</sup> is an aryl group which is optionally substituted, a heterocyclic ring containing N atom(s) which is optionally substituted, a lower alkoxy group which is



optionally substituted or an amino group which is optionally substituted, and  $R^4$ ,  $R^5$ ,  $R^6$  or  $R^7$  optionally combines with  $R^3$  to form a lactone ring represented by the following formula,



wherein, when X is =N-, Y is -CH=N-, or -N=CH-,  $R^2$  is an amino group mono-substituted by a methyl group substituted by an aryl which is optionally substituted, and  $R^3$  is a lower alkyl which is optionally substituted, an amino group mono-substituted by a lower alkyl group substituted by a heterocyclic ring containing N atom(s) which is optionally substituted, or an amino group mono-substituted by a cyclo lower alkyl group which is optionally substituted,  $R^1$  is a lower alkoxy which is optionally substituted, an amino group which is optionally substituted, a hydroxy group which is optionally substituted by a heterocyclic ring containing N atom(s) which is optionally substituted, or cyano group.

Other preferable compounds (I) of the present invention are compounds (I) wherein

X is =CH- or =N-,

Y is -NH-, -NR<sup>4</sup>-, -S-, or -O-,

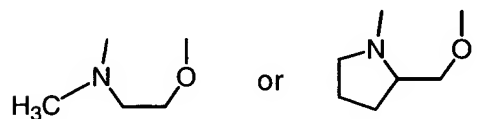
$R^1$  is a lower alkoxy group which is optionally substituted, an amino group which is optionally substituted, a heterocyclic ring containing N atom(s) which is optionally substituted, a hydroxy group which is optionally substituted by a heterocyclic ring containing N atom(s) which is optionally substituted, or cyano group,

$R^2$  is a lower alkylamino group which is optionally substituted by an aryl group which is optionally substituted, a lower alkoxy group which is optionally substituted by an aryl group which is optionally substituted, a lower alkoxy group substituted by an

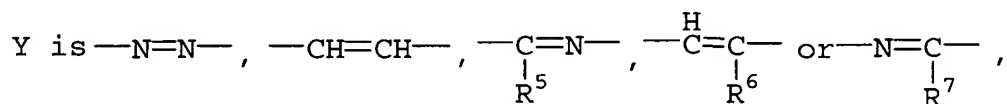
aromatic heterocyclic ring containing N atom(s) which is optionally substituted, a lower alkylamino group substituted by a heterocyclic ring which is optionally substituted, or an amino group substituted by an aryl group which may substituted,

$R^3$  is an aryl group which is optionally substituted, a heterocyclic ring containing N atom(s) which is optionally substituted, a lower alkyl group which is optionally substituted, a lower alkoxy group which is optionally substituted, a cyclo lower alkoxy group which is optionally substituted, a hydroxy group substituted by a heterocyclic ring containing N atom(s) which is optionally substituted, an amino group which is optionally substituted, or

$R^4$  is an aryl group which is optionally substituted, a heterocyclic ring containing N atom(s) which is optionally substituted, a lower alkoxy group which is optionally substituted, or an amino group which is optionally substituted, and  $R^4$  optionally combines with  $R^3$  to form a lactone ring represented by following formula,



Preferable compounds (I) of the present invention are compounds (I) wherein X is =N-,

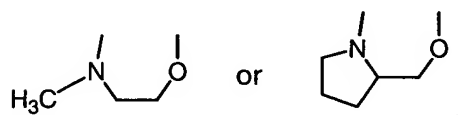


$R^1$  is a lower alkoxy group which is optionally substituted, an amino group which is optionally substituted, a heterocyclic ring containing N atom(s) which is optionally substituted, a hydroxy group which is optionally substituted by a heterocyclic ring containing N atom(s) which is optionally substituted, or cyano group,

$R^2$  is a lower alkylamino group which is optionally substituted by an aryl group which is optionally substituted, a lower alkoxy group which is optionally substituted by an aryl group which is optionally substituted, a lower alkoxy group substituted by an aromatic heterocyclic ring containing N atom(s) which is optionally substituted, a lower alkylamino group substituted by a heterocyclic ring which is optionally substituted, or an amino group substituted by an aryl group which is optionally substituted,

$R^3$  is an aryl group which is optionally substituted, a heterocyclic ring containing N atom(s) which is optionally substituted, a lower alkyl group which is optionally substituted, a lower alkoxy group which is optionally substituted, a cyclo lower alkoxy group which is optionally substituted, a hydroxy group substituted by a heterocyclic ring containing N atom(s) which is optionally substituted, an amino group which is optionally substituted, or

$R^5$ ,  $R^6$  or  $R^7$  is an aryl group which is optionally substituted, a heterocyclic ring containing N atom(s) which is optionally substituted, a lower alkoxy group which is optionally substituted, or an amino group which is optionally substituted, and  $R^5$ ,  $R^6$  or  $R^7$  optionally combines with  $R^3$  to form a lactone ring represented by the following formula,



Preferable compounds (I) of the present invention are compounds (I) wherein

X is =N-,

Y is  $-CH=N-$  or  $-N=CH-$ ,

$R^1$  is a lower alkoxy group which is optionally substituted, an amino group which is optionally substituted, a heterocyclic ring containing N atom(s) which is optionally

substituted, a hydroxy group which is optionally substituted by a heterocyclic ring containing N atom(s) which is optionally substituted, or cyano group,

$R^2$  is a lower alkylamino group which is optionally substituted by an aryl group which is optionally substituted, a lower alkoxy group which is optionally substituted by an aryl group which is optionally substituted, a lower alkoxy group substituted by an aromatic heterocyclic ring containing N atom(s) which is optionally substituted, a lower alkylamino group substituted by a heterocyclic ring which is optionally substituted, or an amino group substituted by an aryl group which is optionally substituted,

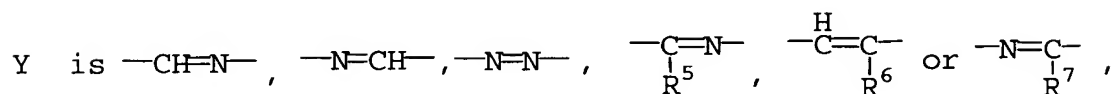
$R^3$  is an aryl group which is optionally substituted, a heterocyclic ring containing N atom(s) which is optionally substituted, a lower alkyl group which is optionally substituted, a lower alkoxy group which is optionally substituted, a cyclo lower alkoxy group which is optionally substituted, a hydroxy group substituted by a heterocyclic ring containing N atom(s) which is optionally substituted, an amino group which is optionally substituted,

provided that when  $R^2$  is an amino group mono-substituted by methyl group substituted by an aryl group which is optionally substituted,

$R^3$  is a lower alkyl group which is optionally substituted, an amino group mono-substituted by a lower alkyl group substituted by a heterocyclic ring containing N atom(s) which is optionally substituted, an amino group mono-substituted by a heterocyclic ring containing N atom(s) which is optionally substituted, or an amino group mono-substituted by a cycloalkyl group which is optionally substituted,  $R^1$  is a lower alkoxy group which is optionally substituted, an amino group which is optionally substituted, a hydroxy group which is optionally substituted by a heterocyclic ring containing N atom(s) which is optionally substituted, or cyano group.

Preferable compounds (I) of the present invention are compounds (I) wherein

X is =CH-,

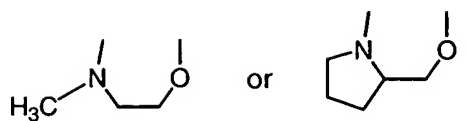


R<sup>1</sup> is a lower alkoxy group which is optionally substituted, an amino group which is optionally substituted, a heterocyclic ring containing N atom(s) which is optionally substituted, a hydroxy group which is optionally substituted by a heterocyclic ring containing N atom(s) which is optionally substituted, or cyano group,

R<sup>2</sup> is a lower alkylamino group which is optionally substituted by an aryl group which is optionally substituted, a lower alkoxy group which is optionally substituted by an aryl group which is optionally substituted, a lower alkoxy group substituted by an aromatic heterocyclic ring containing N atom(s) which is optionally substituted, a lower alkylamino group substituted by a heterocyclic ring which is optionally substituted, or an amino group substituted by an aryl group which may substituted,

R<sup>3</sup> is an aryl group which is optionally substituted, a heterocyclic ring containing N atom(s) which is optionally substituted, a lower alkyl group which is optionally substituted, a lower alkoxy group which is optionally substituted, a cyclo lower alkoxy group which is optionally substituted, a hydroxyl group substituted by a heterocyclic ring containing N atom(s) which is optionally substituted, an amino group which is optionally substituted, or

R<sup>5</sup>, R<sup>6</sup> or R<sup>7</sup> is an aryl group which is optionally substituted, a heterocyclic ring containing N atom(s) which is optionally substituted, a lower alkoxy group which is optionally substituted, or an amino group which is optionally substituted, and R<sup>5</sup>, R<sup>6</sup> or R<sup>7</sup> may combine with R<sup>3</sup> to form a lactone ring represented by following formula,



Preferable compounds (I) of the present invention are compounds (I) wherein

X is =CH-,

Y is -CH=CH-,

R<sup>1</sup> is a lower alkoxy group which is optionally substituted, an amino group which is optionally substituted, a heterocyclic ring containing N atom(s) which is optionally substituted, a hydroxy group which is optionally substituted by a heterocyclic ring containing N atom(s) which is optionally substituted, or cyano group,

R<sup>2</sup> is a lower alkylamino group which is optionally substituted by an aryl group which is optionally substituted, a lower alkoxy group which is optionally substituted by an aryl group which is optionally substituted, a lower alkoxy group substituted by an aromatic heterocyclic ring containing N atom(s) which is optionally substituted, a lower alkylamino group substituted by a heterocyclic ring which is optionally substituted, or an amino group substituted by an aryl group which is optionally substituted,

R<sup>3</sup> is an aryl group which is optionally substituted, a heterocyclic ring containing N atom(s) which is optionally substituted, a lower alkyl group which is optionally substituted, a lower alkoxy group which is optionally substituted, a cyclo lower alkoxy group which is optionally substituted, a hydroxy group substituted by a heterocyclic ring containing N atom(s) which is optionally substituted, an amino group which is optionally substituted.

Preferable compounds (I) of the present invention are compounds (I) wherein

R<sup>1</sup> is

(1) a lower alkoxy group which is optionally substituted by one to three, same or different, substituents selected from the group consisting of a cyclo lower alkyl group, hydroxy group, a lower alkylamino group which is optionally protected, a lower alkoxy group, a hydroxy-substituted lower alkyl group, phenyl group, a lower alkoxyphenyl group, a hydroxy-substituted lower alkylphenyl group, a furyl group, a pyridyl group, a lower alkoxy pyridyl group, a hydroxy-substituted lower alkylpyridyl group, a lower alkylpyridyl group, a pyrimidinyl group, a lower alkoxy pyrimidinyl group, and a morpholinyl group,

(2) a lower alkylamino group which is optionally substituted by one to three, same or different, substituents selected from the group consisting of hydroxy group, a lower alkoxy group, a lower alkyl group, a pyridyl group, a lower alkylamino group, cyano group, a phenyl group which is optionally substituted by a lower alkoxy group and/or a halogen atom, and a hydroxy-substituted lower alkyl group,

(3) an indanylamino group,

(4) a heterocyclic ring containing N atom(s) which is optionally substituted by one to four, same or different, substituents selected from the group consisting of hydroxyl group, a lower alkyl group, a lower alkoxy group, a hydroxy-substituted lower alkyl group, oxo group, a pyridyl group which is optionally substituted by a hydroxy-substituted lower alkyl group, a pyrimidinyl group which is optionally substituted by a lower alkylamino group, formyl group, mesyl group, a lower alkanoyl group substituted by a hydroxy group which is optionally protected, and carbamoyl group,

(5) a hydroxy group which is optionally substituted by a pyridyl group, or

(6) cyano group,

R<sup>2</sup> is

(1) a lower alkylamino group substituted by an aryl group which is optionally substituted by one to four, same or different, substituents selected from the group consisting of a lower alkoxy group, a halogen atom, an amino group, a lower alkanoylamino group, a formylamino group, hydroxy group, a lower alkoxy pyridyl group, a lower alkylamino group, nitro group, a halogeno-substituted lower alkyl group, a lower alkylenedioxy group, cyano group, a lower alkyl group substituted by a hydroxy group which is optionally protected, a lower alkylsulfonyl group, and a lower alkylsulfinyl group,

(2) a lower alkoxy group substituted by one to four, same or different, substituents selected from the group consisting of a lower alkoxy group and a halogen atom,

(3) a lower alkoxy group substituted by a pyridyl group,

(4) a lower alkylamino group substituted by an indolyl group, a pyrimidinyl group, a benzofuranyl group, a dihydrobenzofuranyl group, a lower alkylpyrimidinyl group, a dihydrobenzoxazolyl or a dihydrobenzimidazolyl group, or

(5) an indanylamino group,

$R^3$  is

(1) an aryl group which is optionally substituted by one to four, same or different, substituents selected from the group consisting of a lower alkoxy group and an lower alkylamino group, or an aryl group which is optionally substituted by one or two lower alkylenedioxy groups,

(2) a heterocyclic ring containing N atom(s) which is optionally substituted by one to four, same or different, substituents selected from the group consisting of a lower alkyl group, hydroxy group, an amino group, chlorosulfinyloxy group and a piperidinylloxysulfinyloxy group,



(3) a lower alkyl group which is optionally substituted by one to three, same or different, substituents selected from the group consisting of a morpholinyl group and a di-lower alkoxyphosphoryl group,

(4) a lower alkoxy group which is optionally substituted by one to three, same or different, substituents selected from the group consisting of a pyridyl group, a lower alkoxy pyridyl group, a pyrimidinyl group, a lower alkylamino group, a pyrazinyl group, a lower alkoxy group which is optionally substituted by phenyl group, a pyrimidinyl-substituted oxy group, a pyridyl-substituted oxy group, a pyrimidinyl-substituted lower alkoxy group, a morpholinyl group, a lower alkylmorpholinyl group, a N-lower alkyl-N-pyrimidinylamino group, a lower alkyl dioxolanyl group, a lower alkoxy-substituted lower alkoxy group, a pyridylcarbonylamino group, hydroxy group, and a lower alkylpiperidyl group,

(5) a cyclo lower alkoxy group which is optionally substituted by hydroxy group,

(6) a piperidyl-substituted hydroxy group which is optionally substituted by one to four, same or different, substituents selected from the group consisting of a pyrimidinyl group, a lower alkyl group and a cyano-substituted lower alkyl group, or

(7) an amino group which is optionally substituted by one or two, same or different, substituents selected from the group consisting of

(i) a lower alkoxy group which is optionally substituted by a lower alkoxy group,

(ii) a lower alkyl group which is optionally substituted by one to three, same or different, substituents selected from the group consisting of cyano group, hydroxy group, a lower alkoxy group, a phenyl group which is optionally substituted by a lower alkoxy group and/or a halogen atom, carbamoyl group, a lower alkylamino group, a pyridyl group, a lower alkyl pyridyl group, a lower alkoxy pyridyl group, a pyrimidinyl group, a lower alkoxy pyrimidinyl group, a morpholinyl group, a lower alkyl morpholinyl group, a

hydroxy-substituted lower alkyl morpholinyl group, a cyano- substituted lower alkylmorpholinyl group, a hydroxy-substituted piperidyl group, an oxo-substituted piperazinyl group, a lower alkyl piperazinyl group, a lower alkylsulfonylpiperazinyl group, a pyrrolidinyl group, a lower alkylpyrrolidinyl group, a lower alkylpyrazinyl group, a tetrahydrofuranyl group, a lower alkoxy pyridylamino group, and a pyrimidinylamino group,

(iii) a phenyl group which is optionally substituted by hydroxy group or a lower alkoxy group,

(iv) a pyridyl group which is optionally substituted by a lower alkyl group,

(v) a pyrazolyl group which is optionally substituted by a lower alkyl group,

(vi) an isoxazolyl group which is optionally substituted by a lower alkyl group,

(vii) a morpholinyl group,

(viii) a piperidyl group which is optionally substituted by one to four, same or different, substituents selected from the group consisting of a lower alkoxy carbonyl group, a lower alkylsulfonyl group, a lower alkyl group, a cyano-substituted lower alkyl group, a hydroxy-substituted lower alkanoyl group, formyl group, a lower alkoxy-substituted lower alkanoyl group, and a lower alkylamino-substituted lower alkanoyl group,

(ix) a cyclo lower alkyl group which is optionally substituted by one to three, same or different, substituents selected from the group consisting of a hydroxy group which is optionally protected, a lower alkoxy group, and a pyrimidinyl-substituted oxy group, and

(x) a pyrimidinylamino group which is optionally substituted by a lower alkyl group or a lower alkoxy carbonyl group,

$R^4$ ,  $R^5$ ,  $R^6$  or  $R^7$  is

(1) a phenyl group which is optionally substituted by a lower alkoxy group,

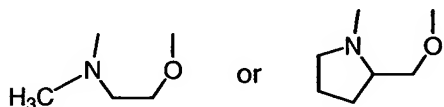
(2) a heterocyclic ring containing N atom(s) which is optionally substituted by hydroxy group, a lower alkyl group or a hydroxy-substituted lower alkyl group,

(3) a lower alkoxy group, or

(4) an amino group which is optionally substituted by a lower alkyl group substituted by a heterocyclic ring containing N atom(s), a hydroxy-substituted cyclo lower alkyl group, or a lower alkyl group, or

$R^4$ ,  $R^5$ ,  $R^6$  or  $R^7$

(5) optionally combines with  $R^3$  to form a lactone ring as shown in following formula;



Preferable compounds (I) of the present invention are compounds (I) wherein

X is =N-,

Y is -S-,

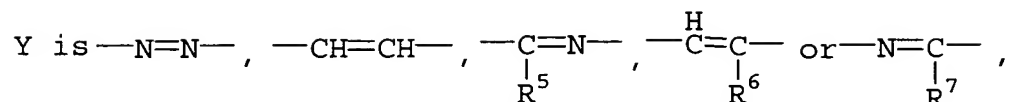
$R^1$  is a pyrrolidinyl group which is optionally substituted by a hydroxy-substituted lower alkyl,

$R^2$  is a lower alkylamino group which is optionally substituted by a phenyl group which is optionally substituted by one or two, same or different, substituents selected from a lower alkoxy group and a halogen atom, and

$R^3$  is an amino group which is optionally substituted by a lower alkoxy group or a pyrimidinyl-substituted lower alkyl group.

Preferable compounds (I) of the present invention are compounds (I) wherein

X is =N-,



R<sup>1</sup> is (1) a lower alkoxy group which is optionally substituted by a lower alkylamino group or a pyridyl group, (2) an amino group which is optionally substituted by hydroxy group or a lower alkoxy group, (3) a heterocyclic ring containing N atom(s) which is optionally substituted by hydroxy group, a lower alkoxy group, a lower alkyl group, a hydroxy-substituted lower alkyl group, oxo group, a pyridyl group which is optionally substituted by a hydroxy-substituted lower alkyl group, or a pyrimidinyl group which is optionally substituted by a lower alkylamino group, or (4) a hydroxy group which is optionally substituted by a pyridyl group,

R<sup>2</sup> is a lower alkylamino group which is optionally substituted by a phenyl group which is optionally substituted by a lower alkoxy group and/or a halogen atom,

R<sup>3</sup> is (1) a lower alkoxy group which is optionally substituted by a phenyl-substituted lower alkoxy group, or (2) an amino group which is optionally substituted by (i) a lower alkyl group which is optionally substituted by the same or different substituents selected from a group of consisting of a lower alkoxy group, a pyridyl group, a lower alkylpyridyl group, a pyrimidinyl group, a lower alkoxypyrimidinyl group, a morpholinyl group, and a lower alkylpyrazinyl group, (ii) a pyridyl group which is optionally substituted by a lower alkyl group, or (iii) a cyclo lower alkyl group which is optionally substituted by hydroxy group,

R<sup>5</sup>, R<sup>6</sup> or R<sup>7</sup> is

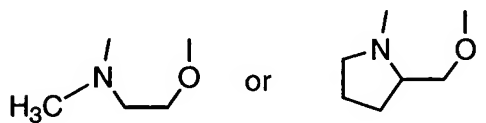
(1) a phenyl group which is optionally substituted by a lower alkoxy group,

(2) a heterocyclic ring containing N atom(s) which is optionally substituted by a hydroxy group, a lower alkyl group or a hydroxy-substituted lower alkyl group,

(3) a lower alkoxy group,

(4) an amino group which is optionally substituted by a lower alkyl group substituted by a heterocyclic ring containing N atom(s), a hydroxy-substituted cyclo lower alkyl group, or a lower alkyl group, or

(5) optionally combines with R<sup>3</sup> to form a lactone ring as shown in following formula,



Preferable compounds (I) of the present invention are compounds (I) wherein

X is =N-,

Y is -CH=N- or -N=CH-,

R<sup>1</sup> is

(1) a lower alkoxy group which is optionally substituted by one to three, same or different, substituents selected from the group consisting of a cyclo lower alkyl group, hydroxy group, a lower alkylamino group which is optionally protected, a lower alkylamino group, a lower alkoxy group, a hydroxy-substituted lower alkyl group, phenyl group, a lower alkoxyphenyl group, a hydroxy-substituted lower alkylphenyl group, a furyl group, a pyridyl group, a lower alkoxypyridyl group, a hydroxy-substituted lower alkylpyridyl group, a lower alkylpyridyl group, a pyrimidinyl group, a lower alkoxypyrimidinyl group, and a morpholinyl group,

(2) a lower alkylamino group which is optionally substituted by one to three, same or different, substituents selected from the group consisting of hydroxy group, a lower alkoxy group, a lower alkyl group, a pyridyl group, a lower alkylamino group, cyano group, a phenyl group which is optionally substituted by a lower alkoxy group and/or a halogen atom, and a hydroxy-substituted lower alkyl group,

(3) an indanylamino group,

(4) a heterocyclic ring containing N atom(s) which is optionally substituted by one to four, same or different, substituents selected from the group consisting of hydroxy group, a lower alkyl group, a lower alkoxy group, a hydroxy-substituted lower alkyl group, oxo group, a pyridyl group which is optionally substituted by a hydroxy-substituted lower alkyl group, a pyrimidinyl group which is optionally substituted by a lower alkylamino group, formyl group, mesyl group, a lower alkanoyl group substituted by a hydroxy group which is optionally protected, and carbamoyl group,

(5) cyano group, or

(6) a hydroxyl group which is optionally substituted by a pyridyl group,

$R^2$  is

(1) a lower alkylamino group substituted by an aryl group which is optionally substituted by one to four, same or different, substituents selected from the group consisting of a lower alkoxy group, a halogen atom, an amino group, a lower alkanoylamino group, a formylamino group, hydroxy group, a lower alkoxy pyridyl group, a lower alkylamino group, nitro group, a halogen-substituted lower alkyl group, a lower alkylenedioxy group, cyano group, a lower alkyl group substituted by a hydroxyl group which is optionally protected, a lower alkylsulfonyl group, and a lower alkylsulfinyl group,

(2) a lower alkylamino group substituted by an indolyl group, a pyrimidinyl group, a benzofuranyl group, a dihydrobenzofuranyl group, a lower alkylpyrimidinyl group, a dihydrobenzoxazolyl group or a dihydrobenzimidazolyl group, or

(3) an indanylamino group,

(4) a lower alkoxy group substituted by an aryl group which is optionally substituted by one to four, same or different, substituents selected from a lower alkoxy group and a halogen atom, or

(5) a lower alkoxy group substituted by a pyridyl group,

R<sup>3</sup> is

(1) an aryl group which is optionally substituted by one to four, same or different, substituents selected from the group consisting of a lower alkoxy group and a lower alkylamino group, or an aryl group which is optionally substituted by one or two lower alkylenedioxy group,

(2) a heterocyclic ring containing N atom(s) which is optionally substituted by one to four, same or different, substituents selected from the group consisting of a lower alkyl group, hydroxy group, an amino group, chlorosulfinyloxy group and a piperidyloxysulfinyloxy group,

(3) a lower alkyl group which is optionally substituted by one to three, same or different, substituents selected from the group consisting of a morpholinyl group and a di-lower alkoxyphosphoryl group,

(4) a lower alkoxy group which is optionally substituted by one to three, same or different, substituents selected from the group consisting of a pyridyl group, a lower alkoxy pyridyl group, a pyrimidinyl group, a lower alkylamino group, a pyrazinyl group, a lower alkoxy group which is optionally substituted by phenyl group, a pyrimidinyl-substituted oxy group, a pyridyl-substituted oxy group, a pyrimidinyl-substituted lower alkoxy group, a morpholinyl group, a lower alkylmorpholinyl group, a N-lower alkyl-N-pyrimidinylamino group, a lower alkyl dioxolanyl group, a lower alkoxy-substituted lower alkoxy group, a pyridylcarbonylamino group, hydroxy group, and a lower alkylpiperidyl group,

(5) a cyclo lower alkoxy group which is optionally substituted by hydroxyl group,

(6) a piperidyl-substituted hydroxy group which is optionally substituted by one to four, same or different, substituents selected from the group consisting of a pyrimidinyl group, a lower alkyl group and a cyano-substituted lower alkyl group, or

(7) an amino group which is optionally substituted by one or two, same or different, substituents selected from the group consisting of

(i) a lower alkoxy group which is optionally substituted by a lower alkoxy group,

(ii) a lower alkyl group which is optionally substituted by one to three, same or different, substituents selected from the group consisting of cyano group, hydroxy group, a lower alkoxy group, a phenyl group which is optionally substituted by a lower alkoxy group and/or a halogen atom, carbamoyl group, a lower alkylamino group, a pyridyl group, a lower alkylpyridyl group, a lower alkoxy pyridyl group, pyrimidinyl group, a lower alkoxy pyrimidinyl group, a morpholinyl group, a lower alkyl morpholinyl group, a hydroxy-substituted lower alkyl morpholinyl group, a cyano-substituted lower alkyl morpholinyl group, a hydroxy-substituted piperidyl group, an oxo-substituted piperazinyl group, a lower alkyl piperazinyl group, a lower alkylsulfonylpiperazinyl group, a pyrrolidinyl group, a lower alkyl pyrrolidinyl group, a lower alkyl pyrazinyl group, a tetrahydrofuranyl group, a lower alkoxy pyridylamino group, and a pyrimidinylamino group,

(iii) a phenyl group which is optionally substituted by hydroxy group or a lower alkoxy group,

(iv) a pyridyl group which is optionally substituted by a lower alkyl group,

(v) a pyrazolyl group which is optionally substituted by a lower alkyl group,

(vi) an isoxazolyl group which is optionally substituted by a lower alkyl group,

(vii) a morpholinyl group,



(viii) a piperidyl group which is optionally substituted by one to four, same or different, substituents selected from the group consisting of a lower alkoxy carbonyl group, a lower alkylsulfonyl group, a lower alkyl group, a cyano-substituted lower alkyl group, a hydroxy-substituted lower alkanoyl group, formyl group, a lower alkoxy-substituted lower alkanoyl group, and a lower alkylamino-substituted lower alkanoyl group,

(ix) a cyclo lower alkyl group which is optionally substituted by one to three, same or different, substituents selected from the group consisting of a hydroxy group which is optionally protected, a lower alkoxy group, and a pyrimidinyl-substituted oxy group, and

(x) a pyrimidinylamino group which is optionally substituted by a lower alkyl group or a lower alkoxy carbonyl group.

Preferable compounds (I) of the present invention are compounds (I) wherein

X is =CH-,

Y is  $\text{—CH=N—}$ ,  $\text{—N=CH—}$ ,  $\text{—N=N—}$ ,  $\text{—}\underset{\text{R}^5}{\text{C}}=\text{N—}$ ,  $\text{—}\overset{\text{H}}{\text{C}}=\underset{\text{R}^6}{\text{C}}\text{—}$  or  $\text{—N}=\underset{\text{R}^7}{\text{C}}\text{—}$ ,

R<sup>1</sup> is a pyrrolidyl group which is optionally substituted by a hydroxy-substituted lower alkyl group,

R<sup>2</sup> is a lower alkylamino group which is optionally substituted by a phenyl group which is optionally substituted by one or two substituents selected from a lower alkoxy group and a halogen atom, and

R<sup>3</sup> is (1) a lower alkoxy group, (2) a lower alkyl group which is optionally substituted by a pyrimidinyl group or a morpholinyl group, or (3) an amino group which is optionally substituted by a cyclo lower alkyl group which is optionally substituted by hydroxy group.

Preferable compounds (I) of the present invention are compounds (I) wherein

X is =CH-,

Y is —CH=CH—,

R<sup>1</sup> is a pyrrolidinyl group which is optionally substituted by a pyridyl-substituted lower alkoxy group or a hydroxy-substituted lower alkyl group,

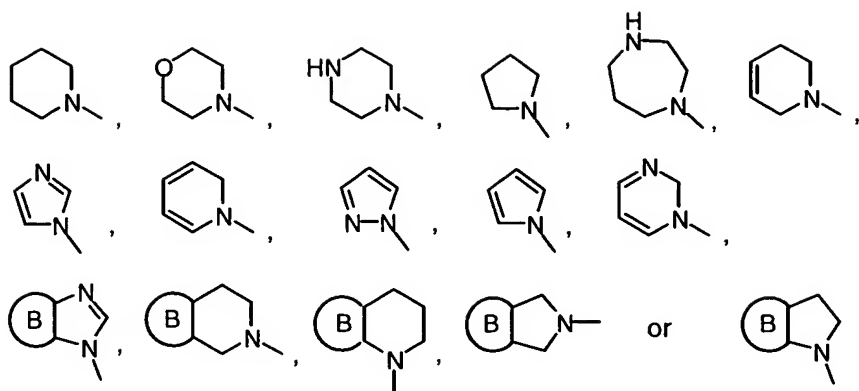
R<sup>2</sup> is a lower alkylamino group which is optionally substituted by an phenyl group which is optionally substituted by one or two substituents selected from a lower alkoxy group and a halogen atom, and

R<sup>3</sup> is (1) a lower alkoxy group, or (2) a lower alkyl group which is optionally substituted by a pyrimidinyl group or a morpholinyl group.

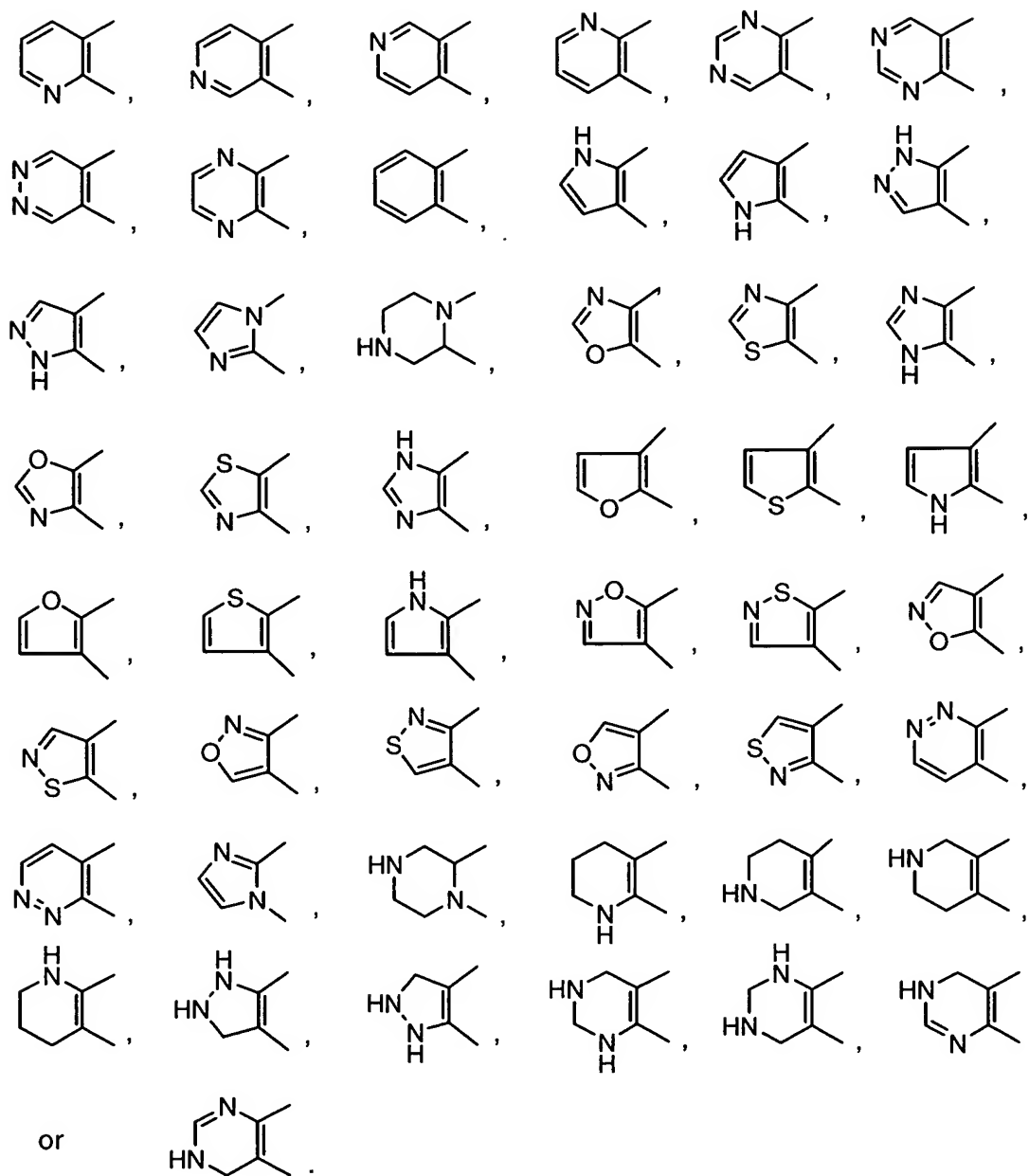
Preferable compounds (I) of the present invention are compounds (I) wherein

an aryl group on R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> or R<sup>7</sup> is a monocyclic, bicyclic or tricyclic 6-14 membered aryl group which may be partially saturated, or a heterocyclic ring containing N atom(s) on R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> or R<sup>7</sup> is a monocyclic or bicyclic 5 to 14 membered heterocyclic containing N atom(s). More concretely, said monocyclic, bicyclic or tricyclic 6-14 membered aryl group which may be partially saturated on R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> or R<sup>7</sup> is phenyl, naphthyl, indenyl or indanyl.

More concretely said monocyclic or bicyclic 5 to 14 membered heterocyclic ring containing N atom(s) on R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> or R<sup>7</sup> is shown as following structures:



wherein ring B is shown as following structures;



Furthermore concretely, said monocyclic or bicyclic 5 to 14 membered heterocyclic ring containing N atom(s) on R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> or R<sup>7</sup> is pyridyl, pyrimidinyl, imidazolyl, piperidyl, pyrazolyl, morpholinyl, piperazinyl, pyrrolidinyl, dihydroisoindolyl, tetrahydroimidazo[1,2-a]pyrazyl, tetrahydroisoquinolyl, dihydro-5-pyrrolo[3,4-b]pyridyl, naphthylidinyl, pyrazo[3,4-d]pyridyl, tetrahydropyridyl, oxazolo[4,5-c]pyridyl, octahydropyrido[3,4-d]pyrimidinyl, thiazolo[4,5-d]pyridyl, imidazo[4,5-d]pyridyl,

perhydrodiazepinyl, perhydropiperadino[3,4-c]piperadinyl, tetrahydroisoxazolo[4,5-c]pyridyl, hexahydropyrazolo[4,3-c]pyridyl, dihydropyridyl, tetrahydroxazolo[5,4-c]pyridyl, hexahydropyrido[3,4-d]pyrimidinyl, octahydropyrido[4,3-d]pyrimidinyl, tetrahydrothiazolo[5,4-c]pyridyl, imidazo[4,5-b]pyridyl, homopiperazinyl, perhydropyrazino[1,2-a]pyrazinyl, tetrahydropyrido[4,3-d]pyrimidinyl, tetrahydrothieno[3,2-c]pyridyl, or tetrahydronaphthylidinyl.

The compound (I) of the present invention or its pharmacologically acceptable salt can be present in form of optical isomers, in case that R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and/or R<sup>7</sup> have an asymmetric carbon atom, and the present invention includes these optical isomers and their mixture.

The compound (I) of the present invention or its pharmacologically acceptable salt has an excellent specific PDEV inhibitory activity, does affect little color sense disorder and blood pressure, and therefore, is useful for prophylactic or therapeutic agents for erectile dysfunction, etc.

The compound (I) of the present invention can be used as a medicine in free base or its acceptable salt. As a pharmacologically acceptable salt of the compound (I), are illustrated inorganic acid salts such as a hydrochloride, a sulfate, a nitrate, a hydrobromide, organic acid salts such as an acetate, a fumarate, an oxalate, a citrate, a methanesulfonate, a benzenesulfonate, a tosylate or a maleate.

The compound (I) of the present invention or its salt includes an intramolecular salt, an additive salt, its solvates or its hydrates.

The compound (I) of the present invention or its pharmacologically acceptable salt is manufactured into traditional pharmaceutical preparations. These preparations

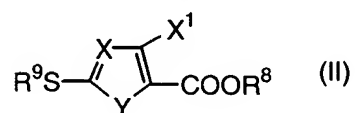
are prepared by a conventional method with additives, such as excipients, binders, poulitices, disintegrants, or fillers.

The compound (I) of the present invention or its pharmacologically acceptable salt is, depending on administration route, age, body weight or situation of the patients, usually administered about 0.001-100mg/kg/day, especially 0.1-10mg/kg/day.

According to the present invention, the compound (I) is prepared by [method A] to [Method D].

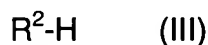
#### [Method A]

The compound (I) of the present invention is prepared by reacting a compound of the following formula(II),



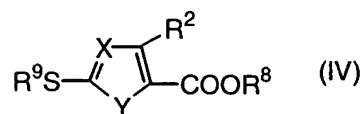
wherein  $\text{X}^1$  is a halogen atom,  $\text{R}^8$  is a protective group of the carboxyl group,  $\text{R}^9$  is a lower alkyl group or an aryl group whose each group is optionally substituted, and X and Y are the same as defined above,

with a compound of the following formula (III),



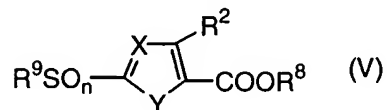
wherein  $\text{R}^2$  is the same as defined above,

to prepare a compound of the following formula (IV),



wherein each symbol is the same as defined above,

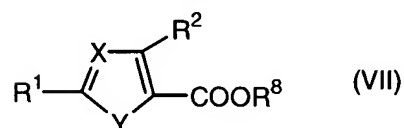
and by oxidizing the compound (IV) to prepare a compound of the following formula (V),



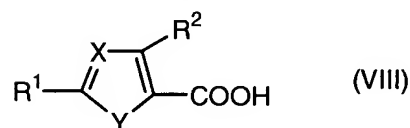
wherein n is 1 or 2, and other symbols are the same as defined above,  
and further, by reacting the compound (V) with a compound of the following formula (VI)  
or a salt thereof,



wherein  $R^1$  is the same as defined above,  
to prepare a compound of the following formula (VII),



wherein each symbol is the same as defined above,  
and then by removing a protective group of the carboxyl group,  $R^8$  to prepare a  
compound of the following formula (VIII),

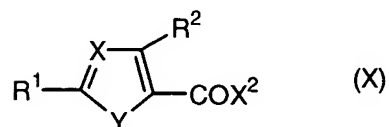


wherein each symbol is the same as defined above,  
and further by reacting the compound (VIII) with a compound of the following formula  
(IX) or its reactive derivative,



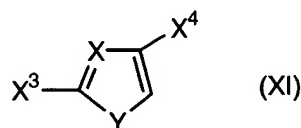
wherein  $R^3$  is the same as defined above,  
to prepare the compound (I).

The compound (I) of the present invention is also prepared by halogenating the  
compound (VIII) to prepare a compound of the following formula (X),



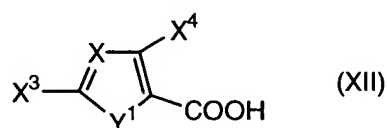
wherein  $X^2$  is a halogen atom and other symbols are the same as defined,  
and then by reacting the compound (X) with a compound (IX) or its reactive derivative.

A compound (VII) wherein Y is -CH=N-, -N=CH- or -N=N-,  
is also prepared by reacting carbon dioxide and a dihalogeno compound of the following  
formula (XI),



wherein X<sup>3</sup> and X<sup>4</sup> are a halogen atom, and X is the same as defined above, and  
Y is -CH=N-,  
-N=CH- or -N=N-,

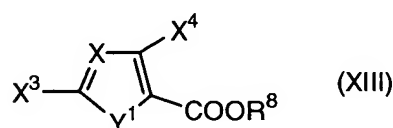
to prepare a compound of the following formula (XII),



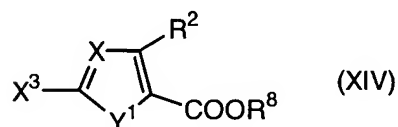
wherein Y<sup>1</sup> is -CH=N-, -N=CH- or -N=N-, and other symbols are the same as  
defined,

and by protecting the carboxyl group of the compound (XII)

to prepare a compound of the following formula (XIII),



wherein the above symbols are the same as defined above,  
and then by reacting the compound (XIII) with a compound (III) to prepare a compound  
of the following formula (XIV),

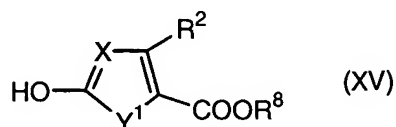


wherein the above symbols are the same as defined above,  
and then by reacting the compound (XIV) with the compound (VI).



A compound (XIV) is also prepared by hydrolyzing a compound (V) wherein Y is -CH=N-, -N=CH- or -N=N-,

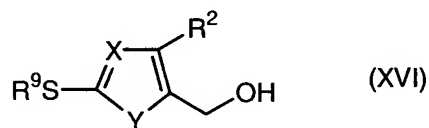
to prepare a compound of the following formula (XV),



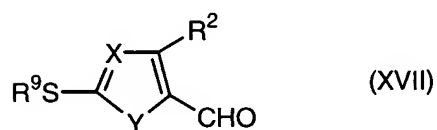
wherein the above symbols are the same as defined above,  
and then by halogenating the compound (XV).

#### [Method B]

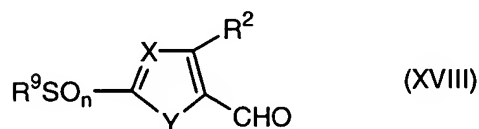
The compound (I) of the present invention is prepared by reducing a compound (IV) to prepare a compound of the following formula (XVI),



wherein the above symbols are the same as defined above,  
and then by oxidizing the compound (XVI) to prepare a compound the following formula (XVII),

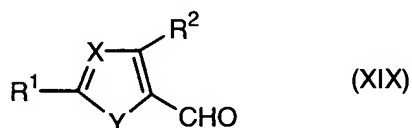


wherein the above symbols are the same as defined above,  
and then, by oxidizing the compound (XVII) to prepare a compound of the following formula (XVIII),



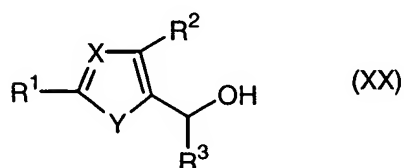
wherein the above symbols are the same as defined above,

and then by reacting the compound (XVIII) with a compound (VI) or its salt, to prepare a compound of the following formula (XIX),



wherein the above symbols are the same as defined above,

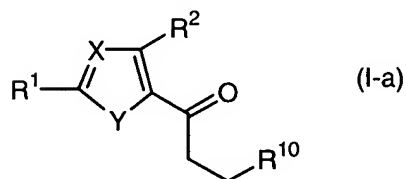
and further by reacting the compound (XIX) with a compound (IX) or its reactive derivative to prepare a compound of the following formula (XX),



wherein the above symbols are the same as defined above,

and then by further oxidizing the compound (XX).

The compound (I) in which R<sup>3</sup> is a lower alkoxy-substituted ethyl group or a morpholino-substituted ethyl group, namely a compound of the following formula (I-a),

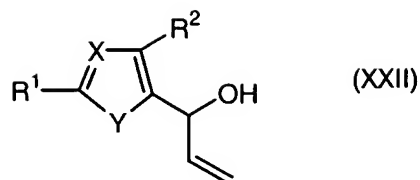


wherein R<sup>10</sup> is a lower alkoxy group or morpholino group, and other symbols are the same as defined above,

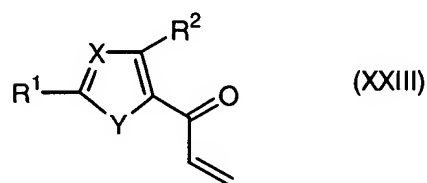
is also prepared by reacting a compound (XIX) and a Grignard agent of the following formula (XXI),



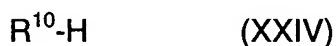
to prepare a compound of the following formula (XXII),



wherein the above symbols are the same as defined above,  
and by oxidizing the compound (XXII) to prepare a compound of the following formula (XXIII),



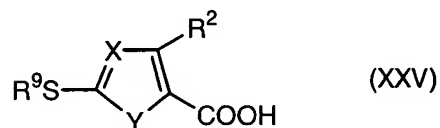
wherein the above symbols are the same as defined above,  
and then by reacting the compound (XXIII) and a compound of the following formula (XXIV) or its salt,



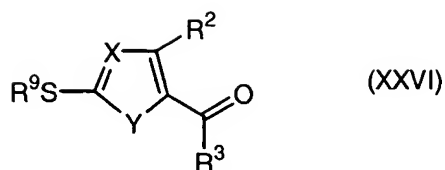
wherein  $R^{10}$  is the same as defined above.

[Method C]

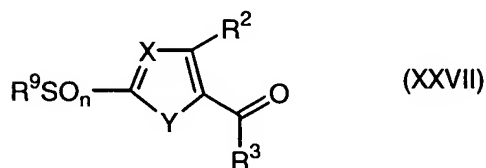
The compound (I) of the present invention is also prepared by reacting a compound of the following formula (XXV),



wherein the above symbols are the same as defined above,  
, which is prepared by deprotecting the protective group ( $R^8$ ) of the carboxyl group of a compound (IV),  
and a compound (IX) or its reactive group to prepare a compound of the following formula (XXVI),

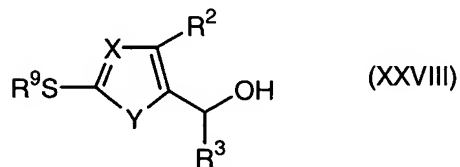


wherein the above symbols are the same as defined above,  
and by oxidizing the compound (XXVI) to prepare a compound of the following formula (XXVII),



wherein the above symbols are the same as defined above,  
and by reacting the compound (XXVII) with a compound (VI) or its salt.

The compound (XXVI) is also prepared by reacting a compound (XVII) and a compound (IX) or its reactive derivative to prepare a compound of the following formula (XXVIII),



wherein the above symbols are the same as defined above,  
and then by oxidizing the compound (XXVIII).

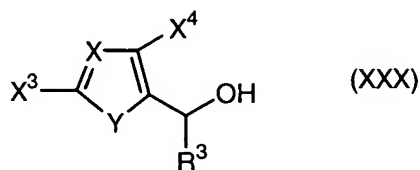
#### [Method D]

The compound (I) is also prepared by reacting a dihalogeno compound (XI) and a compound of the following formula (XXIX),



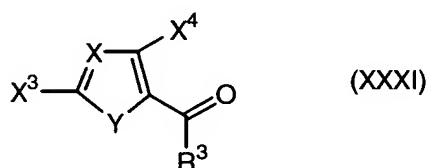
wherein  $R^3$  is the same as defined above,

to prepare a compound of the following formula (XXX),



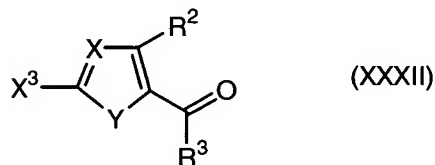
wherein the above symbols are the same as defined above,

and by oxidizing the compound (XXX) to prepare a compound of the following formula (XXXI),



wherein the above symbols are the same as defined above,

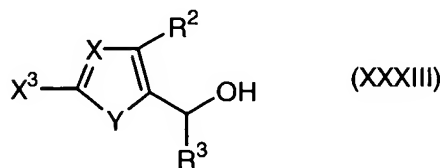
and by reacting the compound (XXXI) with a compound (III) to prepare a compound of the following formula (XXXII),



wherein the above symbols are the same as defined above,

and by reacting the compound (XXXII) with a compound (VI) or its salt.

The compound (XXXII) is also prepared by reacting a compound (XXX) and a compound (III) to prepare a compound of the following formula (XXXIII),

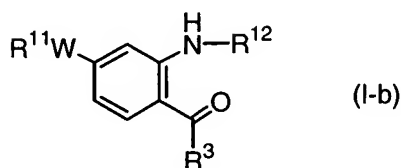


wherein the above symbols are the same as defined above,

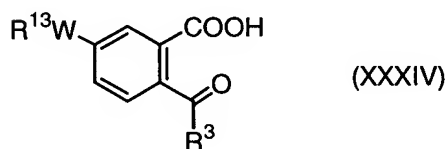
and then by oxidizing the compound (XXXIII).

[Method E]

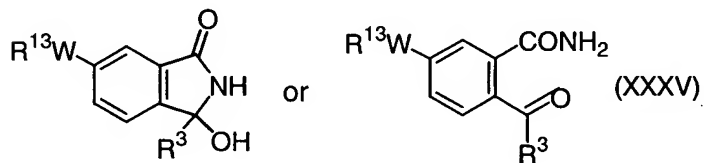
Among the compounds (I) of the present invention, a compound of the following formula (I-b),



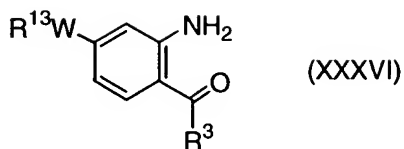
wherein W is immino group or an oxygen atom, R<sup>11</sup> is a lower alkyl group which is optionally substituted, R<sup>12</sup> is an aryl-substituted lower alkyl group which is optionally substituted or a lower alkyl group substituted by an aromatic heterocycle containing N atom(s), and R<sup>3</sup> is the same as defined above, is also prepared by reacting a compound of the following formula (XXXIV),



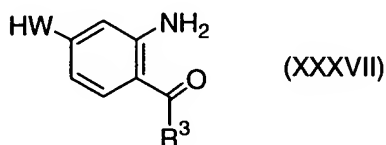
wherein R<sup>13</sup> is a protective group of hydroxy group or a protective group of an amino group, with ammonia to prepare a compound of the following formula (XXXV),



wherein the above symbols are the same as defined above, and by subjecting the compound (XXXV) to Hofmann rearrangement to prepare an aniline compound of the following formula (XXXVI),



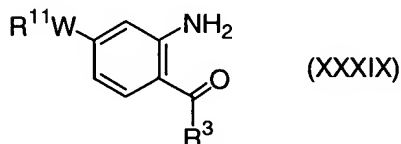
wherein the above symbols are the same as defined above,  
and by deprotecting the protective group  $R^{13}$  to prepare a compound of the following formula (XXXVII),



wherein the above symbols are the same as defined above,  
and by reacting the compound (XXXVII) with a compound of the following formula (XXXVIII),



wherein  $X^5$  is a leaving group and  $R^{11}$  is the same as defined above,  
to prepare a compound of the following formula (XXXIX),

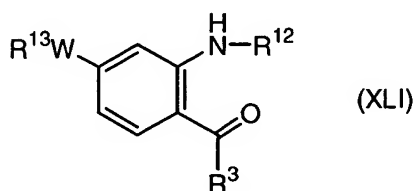


wherein the above symbols are the same as defined above,  
and further, by reacting the compound (XXXIX) with a compound of the following formula (XL),

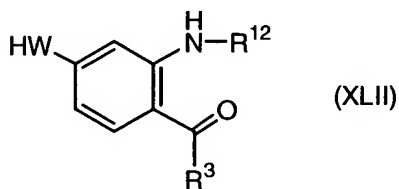


wherein  $X^6$  is a leaving group and  $R^{12}$  is the same as defined above.

The compound (I-b) of the present invention is also prepared by reacting a compound (XXXVI) with a compound (XL) to prepare a compound of the following formula (XLI),



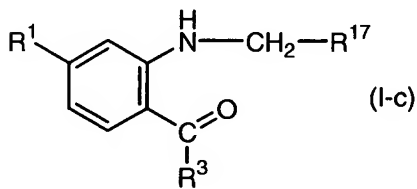
wherein the above symbols are the same as defined above,  
and by deprotecting the protective group R<sup>13</sup> of the compound (XLI) to prepare a compound of the following formula (XLII),



wherein the above symbols are the same as defined above,  
and by reacting the compound (XLII) with a compound (XXXVIII).

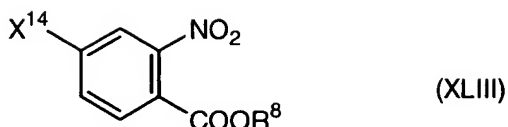
#### [Process F]

Among compounds (I) of the present invention, a compound of the following formula (I-c)

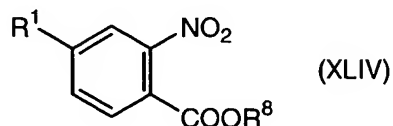


wherein R<sup>17</sup> is an aryl group which is optionally substituted and other symbols are the same as defined above,  
is also prepared by reacting a compound of the following formula (XLIII),

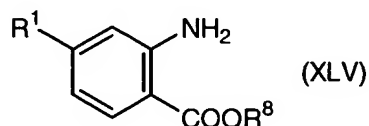




wherein  $X^{14}$  is a halogen atom and  $R^8$  is the same as defined above,  
with a compound (VI) to prepare a compound of the following formula (XLIV),

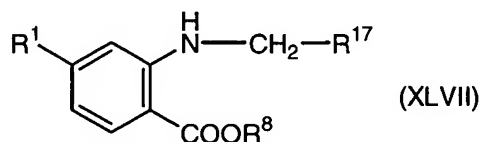


wherein the above symbols are the same as defined above,  
and by reducing the compound (XLIV) to prepare a compound of the following formula (XLV),



wherein the above symbols are the same as defined above,  
and by reacting the compound (XLV) with a compound of the following formula (XLVI),  
 $R^{17}\text{-CHO}$  (XLVI)

wherein the above symbols are the same as defined above,  
to prepare a compound of the following formula (XLVII),

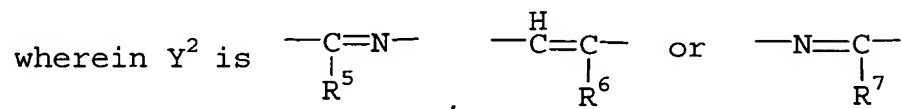
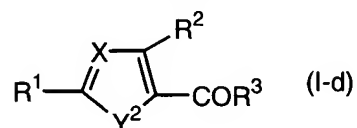


wherein the above symbols are the same as defined above,  
and by deprotecting the protective group ( $R^8$ ) of the compound (XLVII), and then by  
reacting the deprotected compound with a compound (IX) or its reactive derivative.

Furthermore, according to the present invention, a

compound (I) wherein Y is  $\text{—}\overset{\text{H}}{\underset{\text{R}^5}{\text{C}}}=\text{N—}$ ,  $\text{—}\overset{\text{H}}{\text{C}}=\underset{\text{R}^6}{\text{C—}}$  or  $\text{—N}=\underset{\text{R}^7}{\text{C—}}$ ,

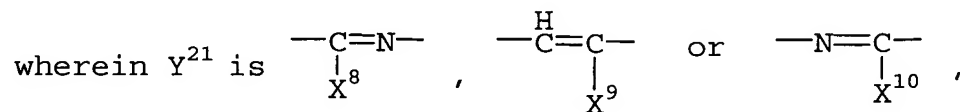
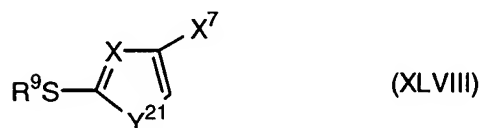
(in which the above symbols are the same as defined above),  
namely a compound of the following formula (I-d),



(in which the above symbols are the same as defined above),  
is prepared by the following methods G to I.

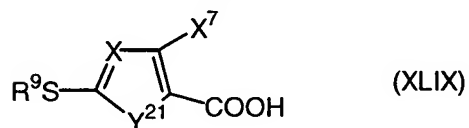
#### [Method G]

A compound (I-d) of the present invention is prepared by treating a compound of the following formula (XLVIII),



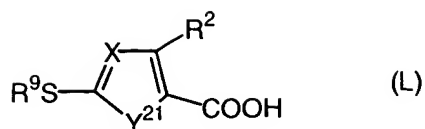
(in which  $\text{X}^7$ ,  $\text{X}^8$ ,  $\text{X}^9$  and  $\text{X}^{10}$  are a halogen atom), and other symbols are the same as define above,

with carbon dioxide to prepare a compound of the following formula (XLIX),

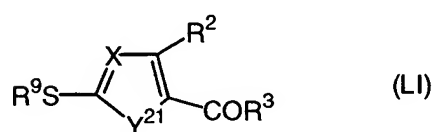


wherein the above symbols are the same as defined above,

and by reacting the compound (XLIX) with a compound (III) to prepare a compound of the following formula (L),



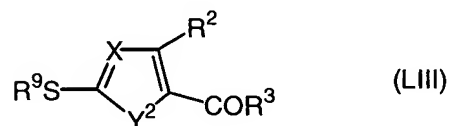
wherein the above symbols are the same as defined above,  
and if necessary, hydrogenating the compound (L) and then by reacting the compound (L) with a compound (IX) or its reactive derivative to prepare a compound of the following formula (LI),



wherein the above symbols are the same as defined above,  
and by reacting the compound (LI) with a compound of the following formula (LII),  
H-R<sup>5-7</sup> (LII)

wherein R<sup>5-7</sup> is R<sup>5</sup>, R<sup>6</sup> or R<sup>7</sup>,

to prepare a compound of the following formula (LIII),

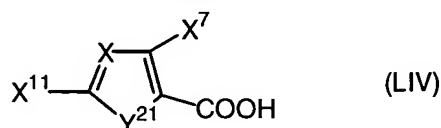


wherein the above symbols are the same as defined above,  
and by oxidizing the compound (LIII),  
and then by reacting the oxidized compound with a compound (VI).

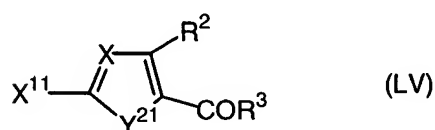
R<sup>3</sup> of a compound (LIII) of the present invention may be converted, if necessary after protecting the carboxyl group of a compound (L). As said protective group, one used in a liquid phase and a usual solid phase carrier such as a merrifield resin may be used. The addition-reaction of the compound (LII) is carried, if desired.

[Method H]

A compound (I-d) of the present invention is prepared by reacting a compound of the following formula (LIV),



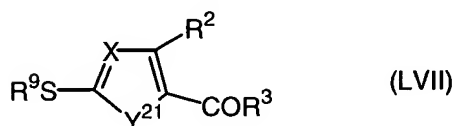
wherein  $X^{11}$  is a halogen atom and other symbols are the same as defined above, and a compound (III), and then by reacting the reactant with a compound (IX) or its reactive derivative to prepare a compound of the following formula (LV),



wherein the above symbols are the same as defined above, and by reacting the compound (LV) with a compound of the following formula (LVI),

$R^9SH$  (LVI)

wherein  $R^9$  is the same as defined above, to prepare a compound of the following formula (LVII),

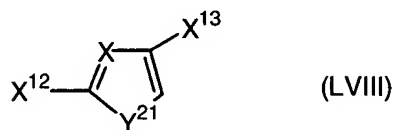


wherein the above symbols are the same as defined above, and by reacting the compound (LVII) with a compound (LII) to prepare a compound (LIII) and by oxidizing the compound (LIII), and then by reacting the oxidized compound with a compound (VI).

The compound (I-d) is also prepared, after reacting a compound (LV) with a compound (LII), by reacting the reactant with a compound (VI), or by reacting the reactant with a compound (LII) after reacting a compound (LV) and a compound (VI).

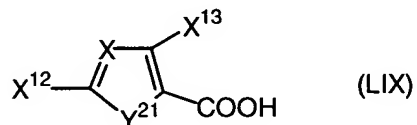
[Method I]

A compound (I-d) of the present invention is prepared by treating a compound of the following formula (LVIII),

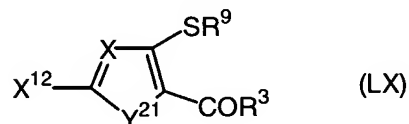


wherein  $X^{12}$  and  $X^{13}$  are a halogen atom, and other symbols are the same as defined above,

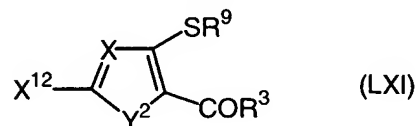
with carbon dioxide to prepare a compound of the following formula (LIX),



wherein the above symbols are the same as defined above,  
and by reacting the compound (LIX) with a compound (LVI),  
and then by reacting the reactant with a compound (IX) or its reactive derivative to  
prepare a compound of the following formula (LX),

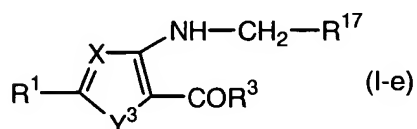


wherein the above symbols are the same as defined above,  
and by reacting the compound (LX) with a compound (LII) to prepare a compound of the  
following formula (LXI),



wherein the above symbols are the same as defined above,  
and by reacting the compound (LXI) with a compound (VI) or its salt and by oxidizing  
the reactant and then by reacting the oxidized compound with a compound (III).

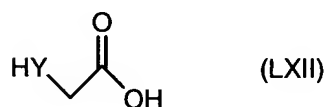
According to the present invention, the compound (I) wherein Y is -NH-, -NR<sup>4</sup>-, -S- or -O-, and R<sup>2</sup> is a lower alkylamino group which is optionally substituted by an aryl group which is optionally substituted, namely a compound of the following formula (I-e),



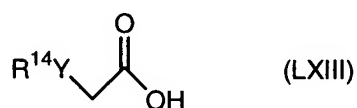
wherein Y<sup>3</sup> is -NH-, -NR<sup>4</sup>-, -S- or -O-, and R<sup>17</sup> is an aryl group which is optionally substituted, and other symbols are the same as defined above,  
is prepared by the following Method J

#### [Method J]

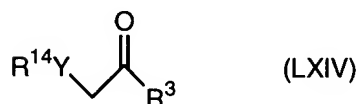
A compound (I-e) of the present invention is prepared by protecting a compound of the following formula (LXII)



wherein the above symbols are the same as defined above,  
to prepare a compound of the formula (LXIII),

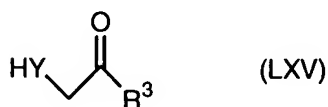


wherein R<sup>14</sup> is a protective group, and Y is the same as defined above,  
and then, by reacting the compound (LXIII) with a compound (IX) or its reactive derivative to prepare a compound of the following formula (LXIV)



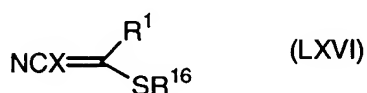
wherein the above symbols are the same as defined above,

and then by deprotecting the compound (LXIV) to prepare a compound of the following formula (LXV),

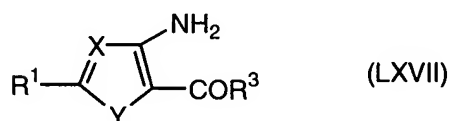


wherein the above symbols are the same as defined above,

and then, by reacting the compound (LXV) with a compound of the following formula (LXVI),



wherein  $\text{R}^{16}$  is a lower alkyl group which is optionally substituted or an aryl group which is optionally substituted, and other symbols are the same as defined above, to prepare a compound of the following formula (LXVII),



wherein the above symbols are the same as defined above,

and by reacting the compound (LXVII) with a compound (XLVI).

Furthermore, according to the present invention, the compound (I) is also prepared by appropriately combining each step in the above methods, and  $\text{R}^1$  of the compound (I) is changed, if desired.

The above methods A-J are practiced as follows:

#### [Method A]

The reaction of a compound (II) and a compound (III) is carried out in a solvent in the presence or absence of an acid scavenger.

As an acid scavenger, is preferably used such as an organic base, such as N,N-diisopropylethylamine, N-methylmorpholine, triethylamine or pyridine, etc., or an inorganic base, such as sodium hydride, sodium carbonate, potassium carbonate or sodium hydrogen carbonate, etc. As a solvent, is preferably used a solvent which does not disturb the reaction, such as dimethyl sulfoxide, tetrahydrofuran, toluene, ethylacetate, chloroform, dimethoxyethane, xylene, N,N-dimethylformamide, acetonitrile, N-methylpyrrolidone, N,N-dimethylacetamide, or dioxane, etc. The reaction of a compound (II) and a compound (III) which are poor in reactivity is preferably carried out in catalyst of a copper reagent such as copper bromide, etc. The reaction preferably proceeds at -10°C to room temperature, especially at 0°C to room temperature.

The oxidation reaction of the compound (IV) to give the compound (V) can be carried out in the presence of an oxidizing agent in a solvent. As an oxidizing agent, is preferably used a peracid, such as m-chloro perbenzoic acid, or peracetic acid, or an inorganic oxidizing agent such as manganese dioxide, sodium periodide, hydrogen peroxide, dinitrogen tetroxide, halogen, hydroperoxide, iodobenzene acetate, tert-butyl hypochlorite, surfuryl chloride, or potassium peroxymonosulfate, etc. As a solvent, is preferably used a solvent which does not disturb the reaction, such as chloroform, methylene chloride, dichloroethane, or acetic acid, etc. The reaction is preferably carried out at -78°C to 50°C, especially -10°C to 10°C.

The reaction of a compound (V) and a compound (VI) or its salt is carried out in a solvent in the presence or absence of an acid scavenger. As an acid scavenger, is preferably used such as an organic base such as N,N-diisopropylethylamine, N-methylmorpholine, triethylamine, or pyridine, etc., or an inorganic base, such as sodium hydride, sodium carbonate, potassium carbonate, cesium carbonate or sodium hydrogen carbonate, etc. As a salt of a compound (VI), is preferably used an alkali



metal salt, such as a sodium salt, or potassium salt, etc. As a solvent, is preferably used a solvent which does not disturb the reaction, such as N,N-dimethylformamide, tetrahydrofuran, dimethoxyethane, dimethyl sulfoxide, acetonitrile, N-methylpyrrolidone, N,N-dimethylacetamide, dioxane, diglyme or dimethoxyethane, etc. The reaction of a compound (V) and a compound (VI) which are poor in reactivity is preferably carried out by addition of palladium(0) catalyst and phosphine ligand. Trisdibenzylidene acetone dipalladium is preferably used as catalyst and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, etc., as phosphine ligand, respectively. The reaction preferably proceeds at 0°C to 250°C, especially at room temperature to 200°C.

In order to prepare a compound (VIII) from a compound (VII) by deprotecting the protective group ( $R^8$ ) of the carboxyl group thereof, the conventional method depending on a kind of the protective groups (e.g. hydrolysis, catalytic reduction, etc.) is properly utilized. In case of deprotection of the protective group by hydrolysis, for example the hydrolysis is carried out in a solvent in the presence of a base. As a base, is preferably used such as an alkali metal hydroxide, such as sodium hydroxide, potassium hydroxide, or lithium hydroxide, etc., or an alkali metal carbonate, such as sodium carbonate, or potassium carbonate, etc. As a solvent, water or a mixture of water and methanol, ethanol, tetrahydrofuran, dioxane, N,N-dimethylformamide, or dimethyl sulfoxide, etc., is properly used. The reaction is preferably carried out at 0°C to 80°C, especially 5°C to 60°C. As a protective group ( $R^8$ ) of the carboxyl group, is used a conventional protective group, such as a lower alkyl group or benzyl group, etc.

The reaction of a compound (VIII) and a compound (IX) or its reactive derivative is carried out in a solvent in the presence or absence of a condensing agent, a base or an activating agent. As a reactive derivative of a compound (IX), is preferably used a halogenated compound or a salt of the compound (IX). As a condensing agent, is

preferably used dicyclohexylcarbodiimido, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimido, diphenylphosphorylazido, or diethylcyanophosphonate, etc., which is usually used in the peptide synthesis. As a base, is preferably used an organic base, such as triethylamine or N-methylmorpholine, etc., and as an activating agent, is preferably used 1-hydroxybenzotriazole, etc. As a solvent, is preferably used a solvents which does not disturb the reaction, such as methylene chloride, tetrahydrofuran, N,N-dimethylformamide, acetonitrile, N,N-dimethylacetamide, ethyl acetate, etc. The reaction is carried out at -30°C to 50°C, especially -10°C to 10°C.

The reaction of a compound (IX) or its reactive derivative with a compound (X), which is prepared from a compound (VIII) as another method, is carried out as follows: first a compound (VIII) is reacted with a halogenating agent in the presence or absence of an activating agent by a conventional method to prepare the compound (X), and then the compound (X) is reacted with the compound (IX). The reaction of the compound (VIII) and a halogenating agent is carried out in a solvent or without a solvent. As a halogenating agent, is preferably used thionyl chloride, oxalyl chloride or phosphorus pentachloride, etc. As an activating agent, is preferably used an amide compound such as N,N-dimethylformamide, or diethylaniline, etc. As a solvent is preferably used a solvent which does not disturb the reaction, such as methylene chloride, chloroform, tetrahydrofuran, benzene, toluene, or dioxane, etc. The reaction is preferably carried out at -30°C to 100°C, especially 5°C to 10°C.

The subsequent reaction of a compound (X) and a compound (IX) is carried out in a solvent in the presence of an acid scavenger. As an acid scavenger, is preferably used an organic base, such as N,N-diisopropylethylamine, N-methylmorpholine, triethylamine, pyridine, dimethylaminopyridine, etc., or an inorganic base, such as

sodium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, etc. As a solvent is preferably used a solvent which does not disturb the reaction, such as tetrahydrofuran, methylene chloride, chloroform, N,N-dimethylacetamide, toluene, benzene, dioxane, or ethyl acetate, etc. The reaction is preferably carried out at -30°C to 100°C, especially 5°C to 10°C.

Further, the reaction to prepare a compound (XII) from a dihalogeno compound (XI) by treating it with carbon dioxide is carried out in a solvent with a base. As a base, is preferably used such as an alkali metal salt of an organic base, such as lithium diisopropylamide, or lithium 2,2,6,6-tetramethylpiperizide, etc. As a solvent, is preferably used a solvent which does not disturb the reaction, such as tetrahydrofuran, 1,2-dimethoxyethane, or diethyl ether, etc. The reaction is preferably carried out at -100°C to -30°C, especially -100°C to -70°C.

The reaction to prepare a compound (XIII) by protecting the carboxyl group of a compound (XII) is carried out by a conventional method. In case that the protective group is a lower alkyl group, the reaction is carried out in the presence of a base and a solvent by adding an alkylating agent to the compound (XII). As an alkylating agent, is preferably used a lower alkyl halide such as methyl iodide. As a base, is preferably used an alkali metal hydrogen carbonate such as sodium hydrogen carbonate, and as a solvent, is preferably used a solvent which does not disturb the reaction, such as N,N-dimethylformamide or tetrahydrofuran, etc. The reaction is preferably carried out at 0°C to 100°C, especially room temperature to 70°C.

The reaction to prepare a compound (XIV) by reacting a compound (XIII) and a compound (III) is carried out in the same manner as the reaction of the compound (II) and the compound (III).

The reaction to prepare a compound (VII) by reacting a compound (XIV) and a compound (VI) is carried out in the same manner as the reaction of the compound (V) and the compound (VI).

The reaction to prepare a compound (XV) from a compound (V) by hydrolyzing it is carried out in a solvent in the presence of a base. As a base, is preferably used such as an alkali metal hydroxide, such as sodium hydroxide, potassium hydroxide, or lithium hydroxide, etc., or an alkali metal carbonate, such as sodium carbonate, or potassium carbonate, etc. As a solvent, is properly used water or a mixture of water and methanol, ethanol, tetrahydrofuran, dioxane, N,N-dimethylformamide, dimethyl sulfoxide, etc. The reaction is preferably carried out at -20°C to 80°C, especially 5°C to 60°C.

The reaction to prepare a compound (XIV) by halogenating a compound (XV) is carried out in the same manner as the reaction to prepare the compound (X) by halogenating the compound (VIII) with a halogenating agent.

#### [Method B]

The reduction of the a compound (IV) to give the compound (XVI) can be carried out in the presence of a reducing agent in a suitable solvent. As a reducing agent, is preferably used such as an alkali metal aluminium hydrate, such as lithium aluminium hydrate, or an alkali metal borohydrate, such as lithium borohydrate. As a solvent, is preferably used such as a solvent which does not disturb the reaction, such as tetrahydrofuran, dioxane, diethyl ether, or dimethoxyethane, etc. The reaction is preferably carried out at -78°C to a boiling point of the solvent, especially -10°C to room temperature.

The oxidation of the compound (XVI) to give the compound (XVII) can be carried out in the presence of an oxidation agent in a solvent. There is no limitation as long as

the oxidizing agent leads an alcohol compound into a carbonyl compound, but is preferably used manganese dioxide, barium per manganate, potassium permanganate, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, pyridinium chlorochromate, or pyridinium dichromate, etc. As a solvent, is preferably used a solvent which does not disturb the reaction, such as chloroform, toluene, ethyl acetate, 1,2-dichloroethane, methylene chloride, or tetrahydrofuran, etc. The reaction is preferably carried out at 0°C to 100°C, especially room temperature to 70°C.

The reaction to prepare a compound (XVIII) by oxidizing a compound (XVII) is carried out in the same manner as the reaction to prepare the compound (V) by oxidizing the compound (IV).

The reaction to prepare a compound (XIX) by reacting a compound (XVIII) and a compound (VI) is carried out in the same manner as the reaction of the compound (V) with a compound (VI).

The reaction to prepare a compound (XX) by reacting a compound (XIX) and a compound (IX) or its reactive derivative is carried out in an appropriate solvent. As a solvent, is preferably used a solvent which does not disturb the reaction, such as tetrahydrofuran, dioxane, diethyl ether, or dimethoxyethane, etc. The reaction is preferably carried out at -78°C to room temperature.

The reaction to prepare the compound (I) by oxidizing a compound (XX) is carried out in the same manner as the reaction to prepare the compound (XVII) by oxidizing the compound (XVI).

Further, the reaction of a compound (XIX) and a Grignard reagent (XXI) is carried out in an appropriate solvent. As a solvent, is preferably used a solvent which does not disturb the reaction, such as tetrahydrofuran, dioxane, or diethyl ether, etc. The reaction is preferably carried out at -78°C to 60°C, especially -78°C to room temperature.

The reaction to prepare a compound (XXIII) by oxidizing a compound (XXII) is carried out in the same manner as the reaction to prepare the compound (XVII) by oxidizing the compound (XVI).

The reaction to prepare a compound (I-a) in which  $R^{10}$  is morpholino by reacting a compound (XXIII) with a compound (XXIV) in which  $R^{10}$  is morpholino group, is carried out in an appropriate solvent in the presence or absence of a base. As a base, is preferably used such as an organic base, such as N,N-diisopropylethylamine, N-methylmorpholine, triethylamine, pyridine, etc., or an inorganic base, such as sodium hydride, sodium carbonate, potassium carbonate, or sodium hydrogen carbonate, etc. As a solvent, is preferably used ethanol, N,N-dimethylformamide, tetrahydrofuran, dimethoxyethane, dimethyl sulfoxide, etc. The reaction is preferably carried out at 0°C to 150°C, especially room temperature to 60°C.

On the other hand, the reaction to prepare a compound (I-a) in which  $R^{10}$  is a lower alkoxy group by reacting a compound (XXIII) with a compound (XXIV) in which  $R^{10}$  is a lower alkoxy group, is carried out in the presence of an acid in a solvent or without a solvent. As an acid, is preferably used an inorganic acid such as sulfuric acid, or an organic acid, such as methane sulfonic acid, camphor sulfonic acid, toluene sulfonic acid or benzene sulfonic acid, etc. As a solvent, is preferably used diethyl ether, toluene, benzene, N,N-dimethylformamide, dimethoxyethane, or dimethyl sulfoxide, etc. The reaction is preferably carried out at 0°C to 150°C, especially room temperature to 60°C.

#### [Method C]

The reaction of removing the protective group ( $R^8$ ) of the carboxyl group of a compound (IV) to give the compound (XXV) is carried out in the same manner as in the

reaction of obtaining the compound (VIII) by removing the protective group ( $R^8$ ) from the carboxyl group of the compound (VII).

The reaction to prepare a compound (XXVI) by reacting a compound (XXV) with a compound (IX) or its reactive derivative is carried out in the same manner as the reaction of the compound (VIII) with the compound (IX) or its reactive derivative.

The reaction to prepare a compound (XXVII) by oxidizing a compound (XXVI) is carried out in the same manner as the reaction to prepare the compound (V) by oxidizing the compound (IV).

The reaction to prepare the compound (I) of the present invention by reacting a compound (XXVII) with a compound (VI) is carried out in the same manner as the reaction of the compound (V) with the compound (VI).

The reaction to prepare a compound (XXVIII) by reacting a compound (XVII) with a compound (IX) or its reactive derivative is carried out in the same manner as the reaction of the compound (XIX) with the compound (IX) or its reactive derivative.

The reaction to prepare a compound (XXVI) by oxidizing a compound (XXVIII) is carried out in the same manner as the reaction to prepare the compound (XVII) by oxidizing the compound (XVI).

#### [Method D]

The reaction to prepare a compound (XXX) by reacting a compound (XI) with a compound (XXIX) is carried out in an appropriate solvent in the presence of a base. As a base, is preferably used such as an alkali metal salt of an organic base, such as lithium diisopropylamide, or lithium 2,2,6,6-tetramethylpiperizide, etc. As a solvent, is preferably used a solvent which does not disturb the reaction, such as tetrahydrofuran,

1,2-dimethoxyethane, or diethyl ether. The reaction is preferably carried out at -100°C to -30°C, especially -100°C to -70°C.

The reaction to prepare a compound (XXXI) by oxidizing a compound (XXX) is carried out in the same manner as the reaction to prepare the compound (XVII) by oxidizing the compound (XVI).

The reaction to prepare a compound (XXXII) by reacting a compound (XXXI) with a compound (III) is carried out in the same manner as the reaction of the compound (II) with the compound (III).

Further, the reaction to prepare the compound (I) of the present invention by reacting a compound (XXXII) with a compound (VI) or its salt is carried out in the same manner as the reaction of the compound (V) with the compound (VI).

The reaction to prepare a compound (XXXIII) by reacting a compound (XXX) with a compound (III) is carried out in the same manner as the reaction of the compound (II) with the compound (III). The reaction to prepare a compound (XXXII) by oxidizing a compound (XXXIII) is carried out in the same manner as the reaction to prepare the compound (XVII) by oxidizing the compound (XVI).

#### [Method E]

The reaction to prepare a compound (XXXV) by reacting a compound (XXXIV) with ammonia is carried out in a presence of a condensing agent in a solvent. Ammonia can be used in an aqueous solution. As a condensing agent, is preferably used a condensing agent used in a conventional peptide synthesis, such as dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, or diisopropylcarbodiimide, etc. As a solvent, is preferably used a solvent which does not disturb the reaction, such as N,N-dimethylformamide, methylene chloride, chloroform,



tetrahydrofuran, etc. The reaction is carried out at -30°C to 50°C, especially 0°C to room temperature.

The reaction to lead a compound (XXXV) into a compound (XXXVI) by subjecting it to Hofmann reaction is carried out in the presence of a base in a solvent with an alkali metal hypohalogenite. As a base, is preferably used sodium hydroxide or potassium hydroxide, etc., and as a solvent, is preferably used a solvent which does not disturb the reaction, such as dioxane, tetrahydrofuran, methylene chloride, acetonitrile, tert-butanol, methanol, ethanol, etc. As an alkali metal hypohalogenite, is preferably used sodium hypochlorite, sodium hypobromite, potassium hypobromite, potassium hypochlorite. The reaction is carried out at -20°C to 100°C, especially 10°C to 60°C.

The reaction to prepare a compound (XXXVII) by deprotecting a compound (XXXVI), or to prepare a compound (XLII) by deprotecting a compound (XLI) is carried out according to the conventional deprotecting method used in the protective group for an amino group or a hydroxyl group. As a protective group for an amino group or a hydroxyl group, is illustrated formyl group, an alkanoyl group (acetyl group, propionyl group, chloroacetyl group, etc.), an aroyl group (benzoyl group, 4-methoxybenzoyl group, etc.), an alkoxycarbonyl group (methoxycarbonyl group, tert-butoxycarbonyl group, etc.), trialkylsilyl group (trimethylsilyl group, tert-butyldimethylsilyl group, etc.), an arylalkoxycarbonyl group (benzyloxycarbonyl group, etc.), an arylalkyl group (benzyl group, 4-methoxybenzyl group, etc.), or tetrahydropyranyl group.

The removal of the protective group of an amino group or a hydroxyl group is carried out by hydrolysis with an acid (e.g. hydrochloric acid, sulfuric acid, phosphoric acid, p-toluensulfonic acid, trifluoroacetic acid, acetic acid, hydrogen fluoride, hydrogen bromide, aluminum chloride, trimethylsilyliodide, trifluoroborate, etc.) or a base (e.g. sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate,

potassium hydrogen carbonate, sodium hydrogen carbonate, ammonia, hydrazine, etc.), by reduction (hydrogen-palladium C, formic acid-palladium C, zinc-acetic acid, metallic sodium-liquid ammonia, etc.), or by oxidation (2,3-dichloro-5,6-dicyano-1,4-benzoquinone(DDQ), hydrogen peroxide, mercury acetate, etc.).

The reaction of a compound (XXXVII) with a compound (XXXVIII) is carried out in the presence of an acid scavenger in a solvent. As an acid scavenger, is preferably used an inorganic base, such as sodium hydroxide, potassium tert-butoxide, potassium carbonate, sodium carbonate, cesium carbonate, potassium hydroxide, sodium hydroxide, sodium methoxide, sodium ethoxide, potassium amide, a lithium amide (e.g. lithium diisopropylamide), etc., an organic base such as N,N-diisopropylethylamine, N-methylmorpholine, triethylamine, pyridine, etc. As a solvent, is preferably used a solvent which does not disturb the reaction, such as tetrahydrofuran, ethanol, methanol, dimethoxyethane, dimethylformamide, toluene, xylene, dimethyl sulfoxide, dimethylacetamide, dioxane, etc. The reaction preferably proceeds at -50°C to boiling point of the solvent, especially at 0°C to 100°C.

The reaction to prepare a compound (I-b) by reacting a compound (XXXIX) with a compound (XL), the reaction to prepare a compound (XLI) by reacting a compound (XXXVI) with a compound (XL), or the reaction to prepare a compound (I-b) by reacting a compound (XLII) with a compound (XXXVIII) is carried out in the same manner as the reaction of the compound (XXXVII) with the compound (XXXVIII).

#### [Method F]

The reaction of a compound (XLIII) with a compound (VI) is carried out in the same manner as the reaction of the compound (V) with the compound (VI).

The reduction of a compound (XLIV) is carried out by the conventional method, for example, preferably by catalytic reduction. The catalytic reduction is carried out for example, at atmospheric pressure under hydrogen gas in a solvent in the presence of catalyst. As catalyst is preferably used palladium-carbon. As a solvent is preferably used ethanol. The reaction proceeds preferably at room temperature.

The reaction of a compound (XLVI) with a compound (XLVI) is carried out in the presence of a reducing agent in a solvent in the presence or absence of an acid, etc. As a reducing agent, is preferably used a sodium triacyloxyborohydride, such as sodium triacetoxymborohydride. As an acid, is an organic acid, such as acetic acid, propionic acid, etc. As a solvent, is preferably used a solvent which does not disturb the reaction, such as dichloro ethane, methylene chloride, tetrahydrofuran, etc. The reaction preferably proceeds at -50°C to 100°C, especially at -10°C to room temperature.

The removal of the protective group ( $R^8$ ) of the carboxyl group of a compound (XLVII) is carried out in the same manner as the removal of the protective group ( $R^8$ ) of the carboxyl group of a compound (VII).

The subsequent reaction of the deprotected compound and a compound (IX) or its reactive derivative is carried out in the same manner as the reaction of a compound(VIII) and a compound (IX) or its reactive derivative.

#### [Method G]

The reaction to prepare a compound (XLIX) by treating a compound (XLVIII) with carbon dioxide is the same manner as the reaction to prepare a compound (XII) by treating a compound (XI) with carbon dioxide.

The reaction to prepare a compound (L) by reacting a compound (XLIX) with a compound (III) is carried out in the same manner as the reaction to prepare a compound (IV) by reacting the compound (II) with the compound (III).

The reaction to prepare a compound (LI) by reacting a compound (L) with a compound (IX), its salt or its reactive derivative is carried out in the same manner as the reaction to prepare a compound (I-a) by reacting the compound (VIII) with the compound (IX) or its reactive derivative. The halogenation of the compound (L) is carried out by the conventional method.

The reaction to prepare a compound (LIII) by reacting a compound (LI) with a compound (LII) is carried out in the same manner as the reaction to prepare the compound (IV) by reacting the compound (II) with the compound (III).

The reaction to prepare a compound (I) by reacting a compound (VI) or its salt after oxidation of a compound (LIII) is carried out in the same manner as the reaction to prepare a compound (I) by reacting the compound (VI) or its salt and the compound (V) prepared by oxidation of the compound (IV).

The protection of the carboxyl group of a compound (L) is carried out in the same manner as the reaction to prepare the compound (XIII) by protecting the carboxy group of the compound (XII). As a solid support, is used a halogenated resin, such as benzylated and phenacylhalogenated resin, etc., as well as merrifield resin.

#### [Method H]

The reaction of a compound (LIV) and a compound (III) is carried out in the same manner as the reaction of the compound (II) and the compound (III). The subsequent reaction of a compound (IX) or its reactive derivative is carried out in the same manner as the reaction of the compound (VIII) and a compound (IX) or its reactive derivative.

The reaction to prepare a compound (LVII) by reacting a compound (LV) and a compound (LVI) is carried out in a solvent in the presence or absence of an acid scavenger.

As an acid scavenger, is preferably used an organic base, such as N,N-diisopropylethylamine, N-methylmorpholine, triethylamine, pyridine, N,N-dimethylaminopyridine, etc., an inorganic base, such as sodium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, cesium carbonate, sodium hydride, etc. As a solvent, is preferably used a solvent which does not disturb the reaction, such as xylene, N,N-dimethylformamide, tetrahydrofuran, dimethoxyethane, dimethyl sulfoxide, toluene, etc. The reaction preferably proceeds at -10°C to room temperature, especially at 0°C to room temperature.

The reaction to prepare a compound (LIII) by reacting a compound (LVII) with a compound (LII) is carried out in the same manner as the reaction to prepare the compound (IV) by reacting the compound (II) with the compound (III).

The reaction with a compound (VI) after oxidation of a compound (LIII) is carried out in the same manner as the reaction to prepare the compound (I) by reacting the compound (VI) or its salt and the compound (V) prepared by oxidation of the compound (IV).

The reaction with a compound (VI) after reacting a compound (LV) and a compound (LII) is carried out in the same manner as the reaction of the compound (LI) with the compound (LII), and the reaction of the compound (V) with the compound (VI).

The reaction with a compound (LII) after reacting a compound (LV) and a compound (VI) is carried out in the same manner as the reaction of the compound (V) with the compound (VI), and the reaction of the compound (LI) with the compound (LII).

#### [Method I]

The reaction to prepare a compound (LIX) by treating a compound (LVIII) with carbon dioxide is the same manner as the reaction to prepare the compound (XII) by treating the compound (XI) with carbon dioxide.

The reaction of a compound (LIX) and a compound (LVI) is carried out in the same manner as the reaction to prepare the compound (LVII) by reacting the compound (LV) with the compound (LVI).

The reaction to prepare a compound (LX) by reacting a compound (IX) or its salt is carried out in the same manner as the reaction to prepare the compound (I) by reacting the compound (VIII) with the compound (IX).

The reaction to prepare a compound (LXI) by reacting a compound (LX) and a compound (LII) is carried out in the same manner as the reaction to prepare the compound (LIII) by reacting the compound (LI) with the compound (LII).

The reaction of a compound (LXI) and a compound (VI) or its salt is carried out in the same manner as the reaction to prepare the compound (VII) by reacting the compound (V) with the compound (VI).

The subsequent oxidation of the compound thus prepared is carried out in the same manner as the oxidation of the compound (IV).

The subsequent reaction to prepare a compound (I-d) by reacting the compound thus obtained with a compound (III) is carried out in the same manner as the reaction to prepare the compound (VII) by reacting the compound (V) and the compound (VI).

#### [Method J]

The reaction to prepare a compound (LXIII) by protection of a compound (LXII) is carried out in the same manner as the reaction to prepare the compound (IV) by

reacting the compound (II) with the compound (III). As a protective group, is used, for example a lower alkyl group which is optionally substituted.

The reaction to prepare a compound (LXIV) by reacting a compound (LXIII) and a compound (IX) or its reactive derivative is carried out in the same manner as the reaction to prepare the compound (I) by reacting the compound (VIII) with the compound (IX) or its reactive derivative.

The reaction to prepare a compound (LXV) by deprotecting a compound (LXIV) is carried out in the same manner as the reaction to prepare the compound (XXXVII) by deprotecting the compound (XXXVI).

The reaction to prepare a compound (LXVII) by reacting a compound (LXV) and a compound (LXVI) is carried out in the presence or absence of a base in a solvent. As a base, is preferably used an organic base, such as N,N-diisopropylethylamine, N-methylmorpholine, triethylamine, pyridine, N,N-dimethylaminopyridine, etc., an inorganic base, such as sodium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, etc. As a solvent, is preferably used a solvent which does not disturb the reaction, such as methanol, ethanol, acetone, N,N-dimethylformamide, tetrahydrofuran, etc. The reaction preferably proceeds at -10°C to 100°C, especially at 60°C to 70°C.

The reaction of a compound (LXVII) and a compound (XLVI) is carried out in the same manner as the reaction of the compound (XLV) with the compound (XLVI).

Thus obtained compound (I) is optionally, formed into its pharmacologically acceptable salt.

The starting material (II) is prepared in accordance with the method described in Journal of American Chemical Society Vol. 65, page 350 (1943)

## Example

Examples of the compound (I) of the present invention which is prepared by the above illustrated methods are illustrated as follows, but thereby the present invention should not be limited.

### Example 1

(1) A 1.6 M solution of n-butyl lithium in hexane (96.5ml, 2.3mol) is added to a solution of diisopropylamine (15.62g, 2.3 mol) in tetrahydrofuran (400ml) over a period of 10 minutes to on a dry ice-acetone bath, and the reaction mixture is stirred for 30 minutes. A solution of 2,4-dichloropyrimidine (10.00g, 1mol) in tetrahydrofuran (350ml) is added thereto over a period of 2 hours, and the mixture is stirred for additional 1 hour. A solution of 3,4,5-trimethoxybenzaldehyde (19.75g, 1.5mol) in tetrahydrofuran (100ml) is added thereto over a period of 1 hour and the mixture is further stirred for 1 hour.

The reaction mixture is poured through a cannula into a mixture (ca. 1.5L) of ice and 10% hydrochloric acid (1.5L) and the mixture is extracted twice with each 500ml of ethyl acetate. The organic layer is collected, washed with 10% hydrochloric acid, water and an aqueous saturated sodium chloride solution, dried over anhydrous sodium sulfate, and condensed in vacuo. The residue is separated by silica gel chromatography (solvent; chloroform: hexane: ethyl acetate = 5:5:2 → hexane: ethyl acetate = 3:1 → 2:1). The desired fraction is collected to condensed in vacuo and the residue is separated by silica gel chromatography (solvent; chloroform: ethyl acetate = 30:1 → 15:1) to be crystallized from n-hexane to give 2,4-dichloro-5-[hydroxy-(3,4,5-trimethoxyphenyl)methyl]pyrimidine 10.83g (yield 47%) as a slightly greenish brown crystalline powder. mp 115-118°C

(2) A mixture of the compound prepared in above (1) 10.83g, manganese dioxide 15g and chloroform 200ml is stirred for 16 hours at room temperature. Further



manganese dioxide 35g and chloroform 60ml are added thereto and the mixture is stirred for 24 hours at room temperature.

After removal of insoluble materials by Celite, the filtrate is concentrated in vacuo. The residue is purified by silica gel chromatography (solvent; hexane: ethyl acetate = 3:1) to be concentrated in vacuo to give 2,4-dichloro-5-(3,4,5-trimethoxyphenylcarbonyl)pyrimidine, 9.30g (yield 86%) as a yellow prism. mp 140-141°C

(3) To a suspension of the compound prepared in above (2) 15g in anhydrous toluene 200ml is added triethylamine 6.63g. A solution of 3-chloro-4-methoxybenzylamine 7.5g in toluene 50ml is added thereto over a period of 20 minutes at 0°C. When the greater part of the amine is added, a white powderish solid precipitates. The mixture is further stirred at room temperature for 1 hour.

After stirring the reaction mixture for 2 hours, 3-chloro-4-methoxybenzylamine 0.75g is further added thereto. The mixture is stirred for additional 1 hour and is filtrated to give a white substance like cake, followed by washing with toluene. The substance like cake consists of a mixture of the desired product and triethylamine hydrochloride. The white cake is dissolved in toluene, and treated with ethyl acetate, tetrahydrofuran and then water and sodium carbonate. The organic layer is washed with an aqueous sodium chloride solution and brine, in order. The solution is dried over anhydrous sodium sulfate and is concentrated.

The residue is dissolved in chloroform, filtered and concentrated in vacuo. The residue is recrystallized from a mixture of chloroform and ether, respectively about 100ml, and the crystals are filtered. Th resulting cake like substances are well washed with ether and dried on air to give 2-chloro-5-(3,4,5-trimethoxyphenylcarbonyl)-4-(3-chloro-4-methoxybenzylamino)pyrimidine 20.21g (yield 97%). mp 165°C

(4) To a solution of 2-(hydroxymethyl)pyridine 68mg in tetrahydrofuran 3ml is added sodium hydride 25mg (60% suspension in oil), and the mixture is stirred for 30 minutes to give a white suspension. A solution of the compound prepared in above (3) 45mg in tetrahydrofuran 3ml is added to the white suspension. During addition color of the suspension is changed to yellow from white. After the mixture is stirred for 1 hour, the reaction mixture is concentrated in vacuo. The residue is poured into ice-water and the mixture is extracted with ethyl acetate. The organic layer is washed with water and brine in order, dried over anhydrous sodium sulfate, and concentrated in vacuo and dried. The residue is purified by silica gel chromatography (solvent; chloroform: methanol = 50:1) to give a single spot on a thin-layer chromatograph.

The desired fraction is evaporated to dryness and the residue is triturated with ethyl acetate-hexane-diisopropyl ether to give 2-(2-pyridylmethoxy)-5-(3,4,5-trimethoxyphenylcarbonyl)-4-(3-chloro-4-methoxybenzylamino) pyrimidine 56.0mg as white crystals. mp 129°C

## Example 2

A solution of 2-methylaminoethanol 100mg in dimethylformamide 1ml is added at room temperature to a solution of 2-chloro-5-(3,4,5-trimethoxyphenylcarbonyl)-4-(3-chloro-4-methoxybenzylamino) pyrimidine (120mg) prepared in above Example 1-(3) in dimethylformamide (1ml). The mixture is stirred at room temperature for 1 hour and thereto is added water 50ml. The mixture is extracted with ethyl acetate-chloroform and the extract is subjected to silica gel chromatography (solvent: chloroform-methanol 5%) to give 2-(N-methyl-N-(2-hydroxyethyl)amino)-5-(3,4,5-trimethoxyphenylcarbonyl)-4-(3-chloro-4-methoxybenzylamino)pyrimidine 110mg as white crystals. mp 166.5-168°C

### Example 3

A mixture of 101mg of 2-chloro-5-(3,4,5-trimethoxyphenylcarbonyl)-4-(3-chloro-4-methoxybenzylamino) pyrimidine prepared in above Example 1-(3), potassium cyanide 27.5mg and palladium chloride triphenylphosphine 3mg in dimethylformamide 3ml is stirred at 120°C for 7 hours. To the reaction mixture is added 4-hydroxypiperidine, and the mixture is stirred at room temperature for 1 hour. The reaction mixture is poured into water and is twice extracted with ethyl acetate. The extract is washed with water and brine in order, dried over anhydrous sodium sulfate and evaporated to dryness to give 2-cyano-5-(3,4,5-trimethoxyphenylcarbonyl)-4-(3-chloro-4-methoxybenzylamino)pyrimidine as a yellow solid, 7.5mg. mp 140-143°C

### Examples 4-45

A compound prepared in Example 1-(3) and the corresponding starting material is treated in the same manner as Example 1-(4) or Example 2 to prepare compounds illustrated in the following Table 1.

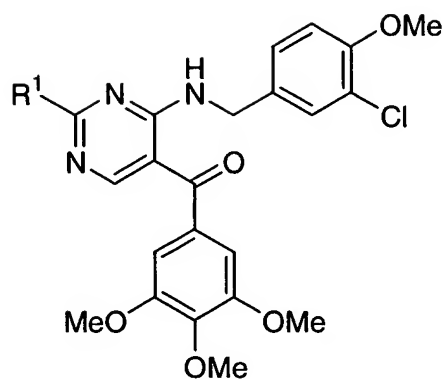
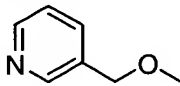
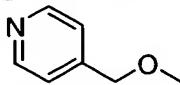
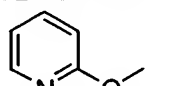
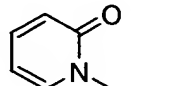
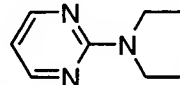
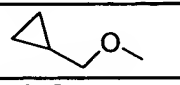
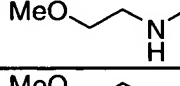
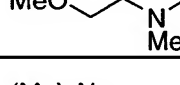
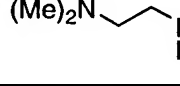
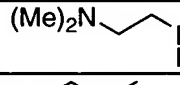
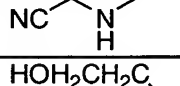
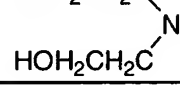


Table 1-1

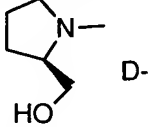
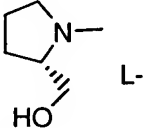
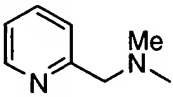
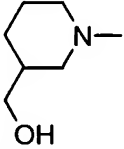
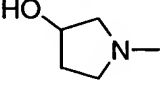
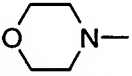
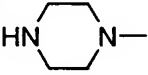
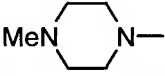
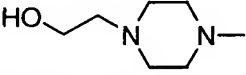
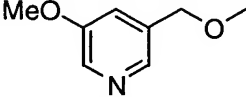
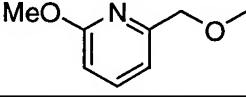
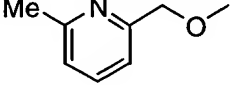
Example No.	$R^1$	Physical Property, etc.
4		mp 98°C
5		mp 112-114°C
6		mp 98°C
7		mp 166-168°C
8		mp 210-201°C
9		mp 132-133°C
10		mp 175-176°C
11		mp 169-170°C
12		mp 129°C

Table 1-2

Example No.	R <sup>1</sup>	Physical Property etc.
13		mp 164-165°C
14		mp 183-184°C
15		Foam IR (nujol): 1622, 3284 cm <sup>-1</sup> MS(m/z): 537(M+H) <sup>+</sup>
16		Foam IR (nujol): 1626, 1675, 3289 cm <sup>-1</sup> MS(m/z): 537(M+H) <sup>+</sup>
17		mp 210-201°C
18	MeO-	mp 136-138°C
19	Me <sub>2</sub> N-	mp 127°C
20		mp 98-100°C
21		mp 166-168°C
22		mp 121-123°C
23*		Powder IR (nujol): 1640 cm <sup>-1</sup> MS(m/z): 544(M+H) <sup>+</sup>
24		mp 112-114°C
25		mp 234-236°C
26		mp 127-129.5°C

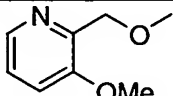
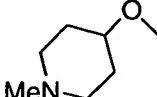
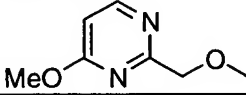
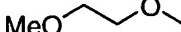

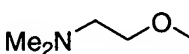
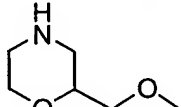
\*trihydrochloride

Table 1-3

Example No.	R <sup>1</sup>	Physical Property etc.
27**		Powder IR (nujol):1637 cm <sup>-1</sup> MS(m/z):543(M+H) <sup>+</sup>
28**		Powder IR (nujol):1636 cm <sup>-1</sup> MS(m/z):543(M+H) <sup>+</sup>
29		mp 139-140°C
30		mp 140-142°C
31		mp 191°C
32		mp 176-177°C
33		mp 155-156°C
34		mp 155-156°C
35		mp 176-178°C
36		mp 154-157°C
37		mp 139-142°C
38		mp 128-131°C

\*\*dihydrochloride

Table 1-4

Example No.	R <sup>1</sup>	Physical Property etc.
39		mp 153-156°C
40		Powder IR (nujol):1645 cm <sup>-1</sup> MS(m/z):557(M+H) <sup>+</sup>
41		mp 128°C
42		mp 113-115°C
43		mp 175-176°C
44		Foam IR (nujol):1619,3304 cm <sup>-1</sup> MS(m/z):531(M+H) <sup>+</sup>
45		Foam IR (nujol):3314,1619 cm <sup>-1</sup> MS(m/z):559(M+H) <sup>+</sup>

# Examples 46-63

A compound prepared in Example 1-(2) and the corresponding starting material is treated in the same manner of Example 1-(3) and Example 1-(4) to prepare compounds illustrated in the following Table 2.

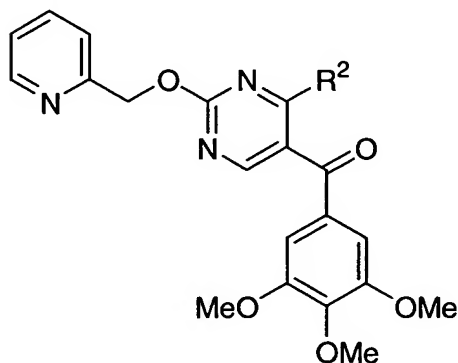
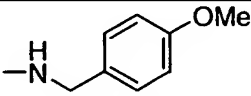
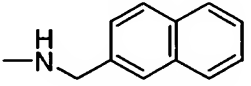
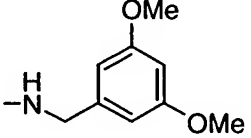
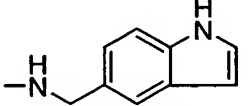
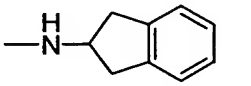
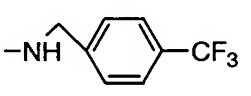
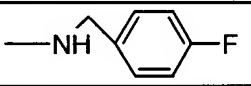
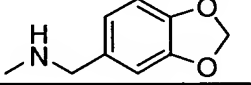
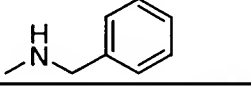
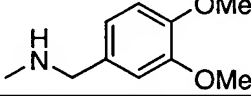
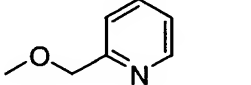


Table 2-1

Example No.	R <sup>2</sup>	Physical Property etc.
46		mp 120-122°C
47		mp 97-99°C
48		mp 149-151°C
49		Amorphous IR (nujol):1621 cm <sup>-1</sup> MS(m/z):560(M+H) <sup>+</sup>
50		mp 124-127°C
51		Amorphous IR (nujol):1621 cm <sup>-1</sup> MS(m/z):565(M+H) <sup>+</sup>
52		mp 136-136.5°C



Table 2-2

Example No.	R <sup>2</sup>	Physical Property etc.
53		mp 91-91.5°C
54		Oil IR (neat):3301,1620 cm <sup>-1</sup> MS(m/z):537(M+H) <sup>+</sup>
55		mp 134-135°C
56		mp 189-191°C
57		Oil IR (neat):3288,1621 cm <sup>-1</sup> MS(m/z):513(M+H) <sup>+</sup>
58		Oil IR (neat):3301,1619 cm <sup>-1</sup> MS(m/z):555(M+H) <sup>+</sup>
59		mp 130-131°C
60		mp 147-148°C
61		mp 119-119.5°C
62		mp 121-122°C
63		mp 153.5-154°C

## Example 64

A mixture of 2-(2-pyridylmethoxy)-5-(3,4,5-trimethoxyphenylcarbonyl)-4-(3-amino-4-methoxybenzylamino)pyrimidine 53mg prepared in Example 47, acetic acid anhydride 8.6mg, pyridine 16mg and methylene chloride 3ml is stirred at room

temperature for 2 hours. To the reaction mixture is further added acetic acid anhydride 8mg and the mixture is stirred for 1.5 hours. To the reaction mixture are added ethyl acetate, water and an aqueous saturated sodium hydrogen carbonate solution in order. The organic layer is separated, washed with brine and dried over anhydrous sodium sulfate.

After filtration of sodium sulfate, the filtrate is concentrated in vacuo. The residue is purified by being subjected to silica gel chromatography (solvent: ethyl acetate → chloroform: methanol = 20:1) and triturated with diethyl ether to give 2-(2-pyridylmethoxy)-5-(3,4,5-trimethoxyphenylcarbonyl)-4-(3-acetylamino-4-methoxybenzylamino)pyrimidine as colorless crystals, 55mg. mp 193.5-195.5°C

#### Example 65

To a solution of 2-(2-pyridylmethoxy)-5-(3,4,5-trimethoxyphenyl-carbonyl)-4-(3-methylamino-4-methoxybenzylamino)pyrimidine (prepared in Example 48) 42mg in methylene chloride 3ml are added mesyl chloride 48mg and triethylamine 69mg, for three times at one hour intervals. The reaction mixture is stirred for 1 hour at room temperature. Ethyl acetate and an aqueous saturated sodium hydrogen carbonate solution is added thereto. The organic layer is separated, washed with brine and dried over anhydrous sodium sulfate. After filtration of sodium sulfate the filtrate is concentrated in vacuo and the residue is purified by preparative thin-layer chromatograph (2 plates, solvent: ethyl acetate) to give 2-(2-pyridylmethoxy)-5-(3,4,5-trimethoxyphenylcarbonyl)-4-[4-methoxy-3-(N-methylmethansulfonylamino)benzylamino] pyrimidine as a colorless amorphous 20mg. IR (Nujol): 1621, 1584cm<sup>-1</sup>  
MS (m/z): 624 (M+H)<sup>+</sup>

#### Example 66

A mixture of 2,4-dichloro-5-(3,4,5-trimethoxyphenylcarbonyl) pyrimidine (prepared in Example 1-(2)) 150mg and 3-chloro-4-methoxyphenylmethanol 79.2mg in tetrahydrofuran 3ml are treated with sodium hydride 19.2mg (suspension in 60% oil) at 0°C for 30 minutes. To the reaction mixture are added 2-pyridylmethanol 47.7mg and sodium hydride 17.5mg (suspension in 60% oil) in order at 0°C. After stirring for 30 minutes, an aqueous sodium hydrogen carbonate solution is added thereto. The mixture is extracted with ethyl acetate and the extract is subjected to preparative thin-layer chromatography to give following compounds:

(A) 2-(3-Chloro-4-methoxybenzyloxy)-5-(3,4,5-trimethoxyphenylcarbonyl)-4-(2-pyridylmethoxy)pyrimidine, 40.1mg, mp 172-173°C.

(B) 2-(2-Pyridylmethoxy)-5-(3,4,5-trimethoxyphenyl carbonyl)-4-(3-chloro-4-methoxybenzyloxy)pyrimidine, 51.9mg, mp 108-109°C.

(C) 2,4-Bis(3-chloro-4-methoxybenzyloxy)-5-(3,4,5-trimethoxyphenylcarbonyl)pyrimidine, 85.7mg, mp 138-139°C.

#### Example 67

(1)-a) A mixture of 2-methylthio-4-chloro-5-ethoxycarbonylpyrimidine 1.0g, (3-chloro-4-methoxyphenyl)methylamine 0.81g, triethylamine 0.66ml and tetrahydrofuran 12 ml is stirred for 4 hours at room temperature. The reaction mixture is diluted with an aqueous 10% citric acid solution and the mixture is extracted twice with ethyl acetate. The combined organic layer is washed with water and an aqueous saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue is purified by silica gel chromatography (solvent; hexane: ethyl acetate = 5:1)

and concentrated in vacuo to give a colorless oil. The oil is left overnight at room temperature to give 2-methylthio-5-ethoxycarbonyl-4-(3-chloro-4-methoxybenzylamino)pyrimidine as crystals, 1.58g. mp 82-83°C.

(1)-b) To a stirred suspension of 2-methylthio-4-chloro-5-ethoxycarbonylpyrimidine (145.0g, 0.62mol) and (3-chloro-4-methoxyphenyl)methylamine (129.0g, 0.62mol) in dimethylformamide (435ml) is added triethylamine (131.8g, 1.30mol) below 20°C. The mixture is stirred at the same temperature for about an hour. After the completion of the reaction, ethyl acetate (1450ml) and water (870ml) are added to the reaction mixture and stirred. The organic layer is separated and washed with water (870ml) and a solution of sodium chloride (72.5g) in water (290ml), and dried over anhydrous magnesium sulfate (29.0g). After removal of the drying agent by filtration and washed with ethyl acetate (145ml), the filtrate and washings are combined and concentrated under reduced pressure. The resultant solid is suspended in 2-propanol (145ml) and the mixture is concentrated under reduced pressure. The resultant solid is dissolved in hot 2-propanol (1450ml) and the solution is seeded with 2-methylthio-5-ethoxycarbonyl-4-(3-chloro-4-methoxybenzylamino)pyrimidine crystals at 55°C. The mixture is cooled down to 45-50°C and continuously stirred at the same temperature for more than an hour. Then the mixture is cooled down below 10°C and continuously stirred for more than 30 minutes. The precipitated crystals are collected by filtration, washed with 2-propanol (145ml) and dried at 50°C for about 16 hours to produce 2-methylthio-5-ethoxycarbonyl-4-(3-chloro-4-methoxybenzylamino)pyrimidine (209.2g, 91%). mp. 86-88°C.

(2) To a solution of 2-methylthio-5-ethoxycarbonyl-4-(3-chloro-4-methoxybenzylamino)pyrimidine (prepared in above (1)-a) 300mg in chloroform 5ml is added under ice cooling m-chloroperbenzoic acid (80%) 369mg. The mixture is stirred

at room temperature for 5 hours. Further m-chloroperbenzoic acid (80%) 106mg and chloroform 6ml are added thereto and the mixture is stirred at room temperature for 2 hours.

The reaction mixture is diluted with an aqueous saturated sodium hydrogen carbonate solution and the water layer is extracted with chloroform. The combined organic layer is washed with water and an aqueous saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue is separated with silica gel chromatography (solvent; hexane: ethyl acetate = 3:1→3:2) to give 2-methylsulfonyl-5-ethoxycarbonyl-4-(3-chloro-4-methoxybenzylamino)pyrimidine as a colorless caramel, 133mg.

IR(CHCl<sub>3</sub>)cm<sup>-1</sup>: 3333, 1695, 1593, 1572, 1503

MS(m/z): 400(M+H)<sup>+</sup>

(3) A mixture of 2-hydroxymethylpyridine 32mg and sodium hydride (suspension in 60% oil) 11.8mg in tetrahydrofuran 2.5ml is stirred at room temperature for 5 minutes. To the mixture is added at room temperature a solution of 2-methylsulfonyl-5-ethoxycarbonyl-4-(3-chloro-4-methoxybenzylamino)pyrimidine (prepared in the above (2)) 118mg in tetrahydrofuran 2.5ml, and the mixture is stirred for 30 minutes at room temperature. The reaction mixture is diluted with an aqueous 10% citric acid solution and extracted twice with ethyl acetate. The combined organic layer is washed with water and an aqueous saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue is purified by silica gel chromatography (solvent; chloroform: ethyl acetate = 4:1→1:2) and concentrated in vacuo to give 2-(2-pyridylmethoxy)-5-ethoxycarbonyl-4-(3-chloro-4-methoxybenzylamino)pyrimidine as a colorless caramel, 106mg.

IR(CHCl<sub>3</sub>)cm<sup>-1</sup>: 3337, 1685, 1591, 1502, 1451, 1440, 1421 MS(m/z): 429(M+H)<sup>+</sup>

### Example 68

(1) To a solution of 2-methylthio-5-ethoxycarbonyl-4-(3-chloro-4-methoxybenzylamino)pyrimidine (prepared in Example 67-(1)) 500mg in chloroform 5ml is dropped a solution of m-chloroperbenzoic acid (80%) 323mg in chloroform 4ml over a period of 30 minutes under ice cooling. The mixture is stirred at the same temperature for 1 hour.

The reaction mixture is diluted with an aqueous saturated sodium hydrogen carbonate solution. The chloroform layer is separated, washed with water and an aqueous saturated sodium chloride solution, dried over anhydrous sodium sulfate and then concentrated in vacuo to give 2-methylsulfinyl-5-ethoxycarbonyl-4-(3-chloro-4-methoxybenzylamino)pyrimidine as a colorless caramel, 545mg.

IR(neat) $\text{cm}^{-1}$ : 3333, 1694, 1588, 1574, 1503, 1463, 1440 MS(m/z): 384(M+H)<sup>+</sup>

(2)-i) A mixture of 2-hydroxymethylpyridine 1,46g, sodium hydride (suspension in 60% oil) 0.521g and tetrahydrofuran 20ml is stirred at room temperature for 20 minutes to prepare a suspension. The resulting suspension is dropped to a solution of the compound (prepared in the above (1)) 4.90g in tetrahydrofuran 25ml over a period of 10 minutes under ice cooling and the mixture is stirred at the same temperature for 1 hour.

The reaction mixture is diluted with an aqueous 10% citric acid solution in ice and the solution is extracted twice with ethyl acetate. The combined organic layer is washed with a 10% aqueous citric acid solution, water and an aqueous saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue is separated by silica gel chromatography (solvent; chloroform: ethyl acetate = 2:1→3:2, then chloroform: methanol = 10:1) and the first fraction is concentrated in vacuo to give 2-(2-pyridylmethoxy)-5-ethoxycarbonyl-4-(3-chloro-4-

methoxybenzylamino)pyrimidine as a slightly yellowish caramel (which is the same compound prepared in Example 67-(3)), 2.25g.

(2)-ii) The second fraction separated by the above silica gel chromatography is concentrated in vacuo, and the residue is subjected to silica gel chromatography (solvent; chloroform: ethyl acetate = 10:1, chloroform: methanol = 10:1) to be divided into the third fraction and the forth fraction.

The third fraction is concentrated in vacuo, and crystallized from isopropyl ether to give 2-(2-pyridylmethoxy)-5-(2-pyridylmethoxycarbonyl)-4-(3-chloro-4-methoxybenzylamino)pyrimidine as a colorless crystalline powder, 234 mg. mp 115-120°C

(2)-iii) The above forth fraction is concentrated in vacuo to give 2-hydroxy-5-ethoxycarbonyl-4-(3-chloro-4-methoxybenzylamino)pyrimidine as a colorless crystalline powder, 2.06g. mp 117-122°C

(3) To a mixture of the compound (prepared in the above (2)-i)) 4.48g in ethanol 80ml and water 40ml is added an aqueous 2N sodium hydroxide solution 52ml under ice cooling, and the reaction mixture is stirred at room temperature for 13 hours. The reaction mixture is neutralized under ice cooling with 10% hydrochloric acid and 10% citric acid, and concentrated in vacuo. The resulting suspension is diluted with water 100ml and left under ice cooling for 30 minutes. The precipitate is collected by filtration and washed with water, isopropyl alcohol, diisopropyl ether and n-hexane, and dried in vacuo at 70°C to give 2-(2-pyridylmethoxy)-5-carboxy-4-(3-chloro-4-methoxybenzylamino)pyrimidine as a colorless crystalline powder, 3.84g. mp 201-203°C

(4) To a solution of the compound (prepared in the above (3)) 51mg in methylene chloride 5ml is added thionyl chloride 10 drops and the mixture is stirred at room

temperature for 1 hour, and volatile substances are removed by vacuum distillation.

The residue is dissolved in methylene chloride 3ml and thereto are added 4-hydroxypiperidine 64mg and triethylamine 89  $\mu$ l. The mixture is stirred at room temperature for 30 minuets.

The reaction mixture is diluted with water and the solution is extracted twice with ethyl acetate. The combined organic layer is washed with an aqueous saturated sodium hydrogen carbonate solution, water and an aqueous saturated sodium chloride solution, dried over anhydrous sodium sulfate and then concentrated in vacuo. The residue is separated by preparative thin-layer chromatography (solvent; chloroform: methanol = 10:1 to give the following three compounds:

(A) 2-(2-Pyridylmethoxy)-5-(4-hydroxypiperidylcarbonyl)-4-(3-chloro-4-methoxybenzylamino)pyrimidine as a colorless amorphous, 27mg.

IR(neat) $\text{cm}^{-1}$ : 3334, 1621, 1614, 1583, 1575, 1503, 1442, 1412

MS(m/z): 484(M+H)<sup>+</sup>

(B) 2-(2-Pyridylmethoxy)-5-(4-chlorosulfinyloxypiperidyl carbonyl)-4-(3-chloro-4-methoxybenzylamino)pyrimidine as a colorless amorphous, 18mg.

IR(nujol) $\text{cm}^{-1}$ : 3333, 1619, 1582, 1501, 1458, 1411

MS(m/z): 466(M+H)<sup>+</sup>

(C) 2-(2-Pyridylmethoxy)-5-[4-(4-piperidyloxysulfinyloxyl) piperidylcarbonyl]-4-(3-chloro-4-methoxybenzylamino) pyrimidine as a colorless amorphous, 3mg.

MS(m/z): 631(M+H)<sup>+</sup>

#### Example 69

A mixture of 2-(2-pyridylmethoxy)-5-carboxy-4-(3-chloro-4-methoxybenzylamino)pyrimidine (prepared in Example 68-(3)) 100mg, 2-hydroxymethylpyrimidine 30mg, 1-(3-



dimethylaminopropyl)-3-ethylcarbodiimido hydrochloride 53mg and dimethylaminopyridine 33mg in dimethylformamide 3ml is stirred at room temperature for 2 hours. The reaction mixture is poured into water and extracted with ethyl acetate. The organic layer is washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue is purified with preparative thin-layer chromatography (solvent; chloroform: methanol = 25:1) and triturated with diethyl ether to give 2-(2-pyridylmethoxy)-5-(2-pyrimidinylmethoxycarbonyl)-4-(3-chloro-4-methoxybenzylamino) pyrimidine 60mg. mp 137-139°C

#### Example 70

(1) A mixture of 2-(2-pyridylmethoxy)-5-carboxy-4-(3-chloro-4-methoxybenzylamino) pyrimidine (prepared in Example 68-(3)) 130mg, methylene chloride 6ml and thionyl chloride 0.10ml is stirred at room temperature for 1 hour. The volatile substances are removed in vacuo and further azeotropic separation thereof is carried out in vacuo by addition of methylene chloride. The residue is diluted with methylene chloride 3ml.

The suspension is divided in two parts, and one part is diluted with methylene chloride 1ml and the mixture is added to methanol 1ml under ice cooling. The reaction mixture is diluted with an aqueous saturated sodium carbonate solution and extracted twice with ethyl acetate. The combined organic layer is washed with an aqueous saturated sodium hydrogen carbonate solution, water and an aqueous saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue is purified with silica gel chromatography (solvent; chloroform: ethyl acetate = 2:1→1:1) and concentrated in vacuo. The resulting residue is triturated with isopropyl ether to give 2-(2-pyridylmethoxy)-5-(methoxycarbonyl)-4-(3-chloro-4-

methoxybenzylamino) pyrimidine as a colorless crystalline powder, 37mg. mp 135-136°C

(2) On the other hand a mixture of the residual part of the above suspension (other part), methylene chloride 3ml and ammonium hydroxide 2ml is stirred under ice cooling for 1 hour. The reaction mixture is diluted with water and extracted twice with ethyl acetate. The combined organic layer is washed with an aqueous 10% sodium hydroxide solution, water and an aqueous saturated sodium chloride solution, dried over anhydrous sodium sulfate and then concentrated in vacuo. The residue is purified with silica gel chromatography (solvent; chloroform: methanol = 20:1→10:1), concentrated in vacuo, and triturated with isopropyl ether to give 2-(2-pyridylmethoxy)-5-(aminocarbonyl)-4-(3-chloro-4-methoxybenzylamino) pyrimidine as a colorless crystalline powder, 45mg. mp 208-209°C

#### Example 71

To a solution of 2-(2-pyridylmethoxy)-5-carboxy-4-(3-chloro-4-methoxybenzylamino) pyrimidine (prepared in Example 68-(3)) 100mg in methylene chloride 3.5ml is added at room temperature thionyl chloride 0.02ml, and the mixture is stirred at room temperature for 1 hour. The volatile substances are removed in vacuo and further azeotropic separation thereof is carried out in vacuo by addition of methylene chloride. The residue is suspended in methylene chloride 8ml. The suspension is added under ice cooling under stirring to a mixture of N-methylmethoxyamine hydrochloride 29mg and an aqueous saturated sodium hydrogen carbonate solution 3ml. The mixture is stirred at room temperature for 1 hour.

The reaction mixture is diluted with water and extracted twice with ethyl acetate. The combined organic layer is washed with an aqueous saturated sodium hydrogen

carbonate solution, water and an aqueous saturated sodium chloride solution, dried over anhydrous sodium sulfate and then concentrated in vacuo. The residue is purified with silica gel chromatography (solvent; ethyl acetate) and concentrated in vacuo to give 2-(2-pyridylmethoxy)-5-(N-methyl-N-methoxyaminocarbonyl)-4-(3-chloro-4-methoxybenzylamino) pyrimidine as a colorless caramel, 81mg.

IR(neat) $\text{cm}^{-1}$ : 3331, 1621, 1581, 1502, 1439, 1410

MS(m/z): 444(M+H)<sup>+</sup>

#### Examples 72-75

A compound prepared in Example 68-(3) and the corresponding starting material is treated in the same manner as Example 69 and Example 70 to prepare compounds illustrated in the following Table 3.

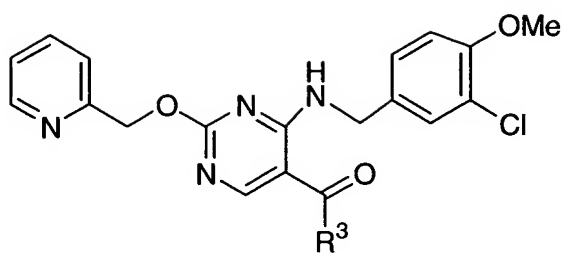


Table 3

Example No.	R <sup>3</sup>	Physical property etc.
72		Amorphous IR:1688 cm <sup>-1</sup> MS(m/z):472(M+H) <sup>+</sup>
73		mp 100-102°C
74		mp 140-142°C
75		mp 128-129°C

#### Example 76

A mixture of 2-(2-pyridylmethoxy)-5-(3,4,5-trimethoxyphenylcarbonyl)-4-(3-chloro-4-methoxybenzylamino) pyrimidine (prepared in Example 1-(4)) 10.0mg, methyl chlorocarbonylacetate 24μl and anhydrous toluene 2ml is reacted for 6 hours at room temperature and for 1 hour at refluxing temperature. The reaction mixture is cooled and thereto are added ethyl acetate and water. The organic layer is separated and washed with water, an aqueous saturated sodium hydrogen carbonate solution and brine in order, dried over anhydrous sodium sulfate and then subjected to silica gel chromatography (solvent; chloroform: ethyl acetate= 1:1 → ethyl acetate) to give 2-

hydroxy-5-(3,4,5-trimethoxyphenylcarbonyl)-4-(3-chloro-4-methoxybenzylamino)pyrimidine as a partial crystalline oil, 6.9mg.

MS(m/z): 458(M-H)<sup>-</sup>

#### Example 77

The compound prepared in Example 68-(1) is dissolved in tetrahydrofuran 40ml, and to the solution are added a mixture of L-prolinol 1.50g and triethylamine 1.60g in tetrahydrofuran 10ml at room temperature. The mixture is stirred overnight and is diluted with ethyl acetate. After washing with an aqueous saturated sodium hydrogen carbonate solution and brine, the organic layer is dried over anhydrous sodium sulfate and the solvent is removed in vacuo. The residue is purified with silica gel chromatography (solvent; chloroform) and crystallized from ether-n-hexane to give (S)-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonyl-2-(2-hydroxymethyl-1-pyrrolidinyl)pyrimidine, 4.72g. mp 88-90°C MS(m/z): 421(M+H)<sup>+</sup>

#### Example 78

2-Methylthio-4-(3-nitro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine as pale yellow crystals, 3.15g (mp 99-100.5°C) is obtained by treating 2-methylthio-4-chloro-5-ethoxycarbonylpyrimidine 2.0g and 3-nitro-4-methoxybenzylamine 1.72g in the same manner as Example 67-(1).

#### Example 79

2-Methylthio-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (prepared in Example 67-(1)) 2.00g is suspended in dimethyl sulfoxide 10ml, and the suspension is treated with a 10% aqueous sodium hydroxide solution 10ml. The

reaction mixture is still in suspension even 6 hours later. After addition of dimethyl sulfoxide 5ml the mixture is stirred at room temperature over night. The resulting clear reaction solution is acidified with citric acid. The excess water (about 50ml) is added thereto and resulting precipitate is filtered, washed with isopropylalcohol and then isopropyl ether, and concentrated in vacuo to give 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-carboxypyrimidine as a pale yellow impalpable powder, 1.864g. mp 238-240°C (decomposition)

#### Example 80

2-Methylthio-4-(3-chloro-4-methoxybenzylamino)-5-carboxypyrimidine (prepared in Example 79) 0.500g, 2-pyridylmethylamine 0.1749g, 1-hydroxybenzotriazole 0.1987g, 1,2-dichloroethane hydrochloride 0.3102g and anhydrous dimethylformamide 5ml are mixed together and stirred at 0°C overnight and triturated with ethyl acetate-isopropyl ether to give 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyridylmethyl)carbamoyl]pyrimidine as a colorless powder, 0.5966g. mp 143-144.5°C

#### Example 81

A mixture of 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-carboxypyrimidine (prepared in Example 79) 0.100g and triethylamine 82µl in tetrahydrofuran 2.0ml is treated under room temperature with 2,4,6-trichlorobenzoyl chloride 51µl and then dimethylaminopyridine about 1mg is added thereto, followed by stirring for 10 minutes. After addition of 2-pyridinemethanol 31µl, the mixture is stirred for 12 hours. Ethyl acetate and water are added thereto and the organic layer is separated, washed with sodium hydrogen carbonate solution, brine. The organic layer is dried over anhydrous sodium sulfate and in vacuo. The residue is purified with silica

gel chromatography (solvent; chloroform: ethyl acetate= 5:1-2:1) and recrystallized from ethyl acetate-isopropyl ether to give 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-(2-pyridylmethoxycarbonyl)pyrimidine as a colorless needle, 0.5183g. mp 117-118°C

#### Example 82

(1) A solution of 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyridylmethyl)carbamoyl]pyrimidine (prepared in Example 80) 150.0mg in chloroform 5.0ml is treated with m-chloroperbenzoic acid (80%) 85.6mg at 0°C for 30 minutes. Piperazine 0.263g is added thereto and the mixture is stirred at room temperature overnight. To the reaction mixture is added ethyl acetate and an aqueous saturated sodium hydrogen carbonate solution, and the organic layer is separated. The organic layer is washed with an aqueous saturated sodium hydrogen carbonate solution, water and a saturated brine, dried over anhydrous sodium sulfate, filtered and then concentrated in vacuo. The residue is purified with silica gel chromatography (solvent; ethyl acetate) to give 2-(1-piperazinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyridylmethyl)carbamoyl]pyrimidine as a colorless amorphous solid, 128.4mg. MS(m/z): 468(M+H)<sup>+</sup>

(2) The compound prepared in the above (1) is treated with hydrochloric acid in methanol to give a crystalline powder, which is triturated with methanol-isopropyl ether to give 2-(1-piperazinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyridylmethyl)carbamoyl]pyrimidine hydrochloride as a colorless crystalline solid, 84.2mg. mp 252-253°C(decomposition)

#### Example 83

2-Methylthio-4-(3-chloro-4-methoxybenzylamino)-5-(2-pyridylmethoxycarbonyl)pyrimidine (prepared in Example 81) 0.1500g is treated with m-chloroperbenzoic acid (80%) 78.9mg at 0°C for 15 minutes. Piperazine 0.2398g is added thereto. The reaction mixture is treated in the same manner as Example 82-(1). The resulting residue is purified with silica gel chromatography (solvent; ethyl acetate sole - ethyl acetate: methanol = 1:1) and recrystallized from ethyl acetate: isopropyl ether (1:1) to give 2-(1-piperazinyl)-4-(3-chloro-4-methoxybenzylamino)-5-(2-pyridylmethoxycarbonyl)pyrimidine as a colorless powder, 75.1mg. mp 101-103°C

#### Example 84

(1) To a suspension of lithium aluminium hydride 4.15g in tetrahydrofuran 150ml is added a solution of 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (prepared in Example 67-(1)) 38.32g in tetrahydrofuran 100ml at 5-10°C under ice cooling over a period of 1 hour. After addition the mixture is stirred for a hour without an ice bath. Water 4.15ml is added under ice cooling thereto, followed by addition of 3N aqueous sodium hydroxide solution 4.15ml. To the mixture is added water 4.15ml three times and the mixture is stirred at room temperature for 1 hour. After treating with magnesium sulfate and filtration, the resulting cake-like substances are washed with tetrahydrofuran. The filtrate is concentrated in vacuo and triturated with ethyl acetate-isopropyl ether. The resulting crystals are filtered and washed well with isopropyl-ether to give 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-hydroxymethylpyrimidine as a pale yellow crystalline powder. The first product; yield 25.10g, mp 162-163°C  
The second product; yield 2.32g, mp 159-160°C



Further the above cake-like substances are again washed with isopropyl ether, and the filtrate is concentrated in vacuo to give colorless crystals. The crystals are suspended in isopropyl ether, and filtered. The precipitates are washed well isopropyl ether and hexane to give 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-hydroxymethylpyrimidine as colorless crystals, 4.26g. mp 161-162°C

(2) To a suspension of 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-hydroxymethylpyrimidine (prepared in the above (1)) 25.10g in chloroform 150ml is a manganese dioxide powder 37.6g ( one and a half of the starting material) and the mixture is vigorously stirred at room temperature for a day. Further the mixture is treated with a manganese dioxide powder 12.6g (a half of the starting material) and the mixture is stirred for three nights. The insoluble materials are filtered off with Celite and the filtrate is concentrated in vacuo. The residue is suspended in ethyl acetate-isopropyl ether. The precipitate is filtered and washed with isopropyl ether and hexane in order, to give 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-formylpyrimidine as colorless crystals, 22.43g. mp 124-125°C

#### Example 85

(1) To a solution of dimethylmethylphosphonate (1.92g) in tetrahydrofuran (10ml) is added a 1.6M solution of n-butyl lithium in hexane (8.69ml) at -78°C over a period of 10 minutes, and the mixture is stirred at the same temperature for 30 minutes. A solution of 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-formylpyrimidine (prepared in Example 84-(2)) 1.00g in tetrahydrofuran 10ml is dropped by a syringe at -78°C to the reaction mixture to give a yellow suspension. The suspension is stirred for 30 minutes. After removal of a dry ice-acetone bath the reaction mixture is stirred for a while and poured into an aqueous saturated sodium hydrogen carbonate solution. The

mixture is stirred and extracted with ethyl acetate. The organic layer is separated, washed with water and brine in order, dried over anhydrous sulfate and concentrated in vacuo to give crude 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-[(1-hydroxy-2-dimethoxyphosphoryl)ethyl]pyrimidine as a colorless foam, 1.33g.

(2) A mixture of crude 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-[(1-hydroxy-2-dimethoxyphosphoryl)ethyl]pyrimidine (prepared in the above) 1.32g, manganese dioxide 3.96g and chloroform 20ml is vigorously stirred at room temperature overnight. The insoluble manganese dioxide is filtered off and the filtrate is concentrated in vacuo to give a pale yellow foam. The residue is purified with silica gel chromatography (solvent; ethyl acetate sole - ethyl acetate: methanol = 10:1). The purified fraction is collected and concentrated in vacuo to give a colorless foam, 1.18g. The compound is crystallized from ethyl acetate-isopropyl ether to give 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-(dimethoxyphosphorylacetyl)pyrimidine as colorless crystals, 1.14g. mp 104-105°C

#### Example 86

(1) To a 1.6M solution of n-butyl lithium in hexane 2.0ml is dropped a solution of 3-bromopyridine 530mg in diethyl ether 2ml by a syringe in a dry ice-acetone bath. A white solid immediately occurs. The reaction mixture is stirred at -78°C for 10 minutes. To the reaction mixture is added by a syringe a solution of 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-formylpyrimidine 208mg in tetrahydrofuran 2ml. The mixture is irradiated with ultrasonic wave for several seconds. The reaction mixture is stirred at -78°C for 5 minutes, and an aqueous saturated sodium hydrogen carbonate solution is added thereto. The mixture is extracted with ethyl acetate and the organic layer is washed with water and brine in order, dried over sodium sulfate and concentrated in

vacuo to give a yellow oil. The crude compound is purified with silica gel chromatography (silica gel 20g, solvent; ethyl acetate sole - ethyl acetate: methanol = 20:1) to give 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-[(hydroxy)(3-pyridyl)methyl]pyrimidine as a yellow foam, 155mg. MS(m/z): 403(M+H)<sup>+</sup>

(2) A mixture of 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-[(hydroxy)(3-pyridyl)methyl]pyrimidine (prepared in the above) 149mg and manganese dioxide 450mg in chloroform 3ml is stirred at room temperature overnight. After removal of insoluble substances by filtration, the filtrate is concentrated in vacuo to give a slightly yellowish solid 140mg. The solid is suspended in ethyl acetate-isopropyl ether and filtered. The resulting cake-like substances are well washed with hexane to give 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-(3-pyridylcarbonyl)pyrimidine as colorless crystals, 127mg. mp 141-142°C. MS(m/z): 401(M+H)<sup>+</sup>

#### Example 87

A solution of 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-formylpyrimidine (prepared in Example 84-(2)) 2.057g in chloroform 20ml is treated at 0°C for 30 minutes with m-chloroperbenzoic acid (80%) 1.468g. L-(S)-Prolinol 0.901g and then triethylamine 1.33ml are added thereto. The reaction is carried out at 0°C for 1 hour. The reaction mixture is elevated to room temperature, diluted with ethyl acetate, washed with an aqueous sodium hydrogen carbonate solution, water and a saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The precipitate is filtered off and the filtrate is concentrated in vacuo to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-formylpyrimidine as a colorless amorphous, 1.9990g. MS(m/z): 377(M+H)<sup>+</sup>

#### Example 88

A solution of 4-(3-chloro-4-methoxybenzylamino)-5-formyl-2-methylthiopyrimidine 0.5g in tetrahydrofuran 20ml is reacted at -78°C with lithium salt of 1-methylimidazole 0.394ml in the same manner as Example 86 to give 4-(3-chloro-4-methoxybenzylamino)-5-[(hydroxy)(1-methyl-2-imidazolyl)methyl]-2-methylthiopyrimidine. Thus obtained compound is oxidized at room temperature with manganese dioxide in chloroform and then the oxidized compound is post-treated in the same manner as Example 86 to give 4-(3-chloro-4-methoxybenzylamino)-5-(1-methyl-2-imidazolylcarbonyl)-2-methylthiopyrimidine 0.5913g. mp 158-159°C

#### Example 89

A solution of the compound (prepared in Example 88) 124.0mg in chloroform 3.0ml is treated under stirring under ice cooling for 15 minutes with 80% m-chloroperbenzoic acid 69.5mg in the same manner as Example 87. To the mixture are added L-prolinol 60.6μl and triethylamine 86μl, and the mixture is stirred under room temperature overnight and post-treated in the same manner as Example 87, to give (S)-4-(3-chloro-4-methoxybenzylamino)-2-(2-hydroxymethyl-1-pyrrolidinyl)-5-(1-methyl-2-imidazolylcarbonyl)pyrimidine 121.2mg.

IR(CHCl<sub>3</sub>)cm<sup>-1</sup>: 3291, 1591, 1527, 1456, 1417, 1409, 1269, 1063, 805

MS(m/z): 457(M+H)<sup>+</sup>

#### Example 90

(1) To a 1.6 M solution of n-butyl lithium in hexane 19.3ml is dropped over a period of 10 minutes a solution of diisopropylamine 3.1g in tetrahydrofuran 80ml in a dry ice-acetone bath and the mixture is stirred for 30 minutes. To the mixture is dropped

over a period of 2.5 hours a solution of 2,4-dichloropyrimidine 2g in tetrahydrofuran 70ml and the mixture is stirred at the same temperature for 1 hour. To the mixture is dropped pyridine-2-aldehyde 2.2g in tetrahydrofuran 20ml over a period of 50 minutes, and the mixture is stirred at the same temperature for 1 hour. The reaction mixture is poured into a 10% aqueous citric acid solution and the organic layer is separated, washed with water and brine, dried over sodium sulfate and concentrated in vacuo. The residue is purified with silica gel chromatography (solvent; chloroform: methanol = 10:1, hexane: ethyl acetate= 3:2, hexane: ethyl acetate= 2:1) to give crude 2,4-dichloro-5-[(hydroxy)(2-pyridyl)methyl]pyrimidine 480mg.

(2) A mixture of the crude compound (prepared in the above (1)) 104mg, triethylamine 71mg and 3-chloro-4-methoxybenzylamine 44mg in toluene 2ml is stirred for 12 hours at room temperature. The reaction mixture is poured into water and extracted with ethyl acetate. The organic layer is washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue is purified with preparative thin-layer chromatography (solvent; chloroform: methanol = 22:1) to give 2-chloro-4-(3-chloro-4-methoxybenzylamino)-5-[(hydroxy)(2-pyridyl)methyl]pyrimidine as an amorphous 53mg. MS(m/z): 391(M+H)<sup>+</sup>

(3) A mixture of 2-chloro-4-(3-chloro-4-methoxybenzylamino)-5-[(hydroxy)(2-pyridyl)methyl]pyrimidine (prepared in the above (2)) 46mg, manganese dioxide 230mg and chloroform 2.3ml is stirred at room temperature for 3 hours. After removal of insoluble substances by filtration, the filtrate is concentrated in vacuo to give 2-chloro-4-(3-chloro-4-methoxybenzylamino)-5-(2-pyridylcarbonyl)pyrimidine 39mg. mp 117-119°C (recrystallization from diethyl ether), MS(m/z): 389(M+H)<sup>+</sup>

Example 91

A mixture of 2-chloro-4-(3-chloro-4-methoxybenzylamino)-5-(2-pyridylcarbonyl)pyrimidine (prepared in Example 90-(3)) 110mg, 2-pyridinemethanol 34mg, 10% sodium hydride 12mg and tetrahydrofuran 3ml is stirred at room temperature for 5 minutes. The reaction mixture is poured into water and extracted with ethyl acetate. The organic layer is washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue is purified by silica gel chromatography (solvent: ethyl acetate) and triturated with ethyl ether to give 2-(2-pyridylmethoxy)-4-(3-chloro-4-methoxybenzylamino)-5-(2-pyridylcarbonyl)pyrimidine, 104mg. mp 81-84°C, MS(m/z): 462(M+H)<sup>+</sup>

#### Example 92

To a solution of a whole amount of 2-methylsulfinyl-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (prepared in Example 68-(1)) in tetrahydrofuran 6ml is dropped 2N aqueous sodium hydroxide solution 1.32ml under ice cooling over a 2 minute period and the reaction mixture is stirred at the same temperature for 30 minutes. Further tetrahydrofuran 8ml and N,N-dimethylacetamide 6ml are added thereto and the mixture is stirred under ice cooling for 30 minutes. Thereto are added water 5ml and N,N-dimethylacetamide 2ml and the mixture is stirred under ice cooling for one hour. The reaction mixture is acidified with an aqueous 10% citric acid solution and diluted with water, extracted twice with ethyl acetate. The combined organic layer is washed with water and an aqueous saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue is separated by silica gel chromatography (silica gel 20g, solvent; chloroform: ethyl acetate = 5:1 → chloroform: isopropanol = 30:1) to give 2-hydroxy-4-(3-chloro-4-

methoxybenzylamino)-5-ethoxycarbonylpyrimidine as a slightly yellowish crystalline powder, 618mg. mp 195-197°C

#### Example 93

To a solution of 2-methylsulfinyl-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (prepared in Example 68-(1)) 200mg in tetrahydrofuran 4ml is added under ice cooling potassium tert-butoxide 58mg, and the reaction mixture is stirred at the same temperature for 1 hour. The reaction mixture is diluted with an aqueous citric acid solution, extracted twice with ethyl acetate. The combined organic layer is washed with water and an aqueous saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue is purified by silica gel chromatography (silica gel 10g, solvent; chloroform sole → chloroform: methanol= 20:1) to give the following two fractions.

The first fraction is concentrated in vacuo to give 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine as a slightly brown oil, 33mg.

The second fraction is concentrated in vacuo to give 2-hydroxy-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine as a slightly brown crystalline powder, 132mg. mp 195-197°C

#### Example 94

A mixture of 2-hydroxymethylpyrimidine 1M tetrahydrofuran 0.29ml, sodium hydride(60%) 11mg in tetrahydrofuran 1.5ml is stirred at room temperature for 10 minutes. To the mixture is added 2-methylsulfinyl-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (prepared in Example 68-(1)) 100mg in tetrahydrofuran 2ml, and the mixture is stirred at room temperature for 30 minutes. To the reaction mixture

are added water 2ml, ethanol 2m and 2N aqueous sodium hydroxide solution 3ml, and the mixture is stirred at room temperature overnight.

The reaction mixture is neutralized with a 10% aqueous citric acid solution, and tetrahydrofuran and ethanol are removed in vacuo. The precipitate is collected, washed with water to give a colorless powder. The powder is dissolved in a mixture of 10% aqueous sodium hydroxide solution and ethyl acetate and the water layer is separated and washed with ethyl acetate. The water layer is neutralized with 10% hydrochloric acid and a 10% aqueous citric acid solution. The resulting precipitate is collected and washed with water to give 2-(2-pyridylmethoxy)-4-(3-chloro-4-methoxybenzylamino)-5-carboxypyrimidine as a colorless powder, 28mg. mp 204-206°C

On the other hand, the combined organic layer after removal of the water layer from the above reaction mixture, is washed with 10% aqueous sodium hydroxide solution, water and an aqueous saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated in vacuo to give 2-hydroxy-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine as a colorless crystalline powder, 17mg. mp 195-197°C, MS(m/z): 338(M+H)<sup>+</sup>

#### Example 95

A mixture of 2-hydroxy-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (prepared in Example 92) 500mg, diethylaniline 2ml and phosphoryl chloride 4ml is stirred at 80°C for 30 minutes and then at 100°C for 5 hours. After cooling, the reaction solution is poured into water in ice and the mixture is stirred at room temperature for 30 minutes. The product is extracted with ethyl acetate and the organic layer is washed with water and an aqueous saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue is purified



by silica gel chromatography (silica gel 7g, solvent; chloroform) to give 2-chloro-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine as a slightly yellow crystalline powder, 375mg. mp 114-115°C MS(m/z): 356(M+H)<sup>+</sup>

#### Example 96

To a solution of 2-chloro-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (prepared in Example 95) 356mg and 2-hydroxymethylpyridine 109mg in anhydrous tetrahydrofuran 4.5ml is added potassium tert-butoxide 112mg under ice cooling, and the mixture is stirred for 30 minutes. The reaction mixture is diluted with water, extracted twice with ethyl acetate. The combined organic layer is washed with water and an aqueous saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue is purified by silica gel chromatography (silica gel 10g, solvent; chloroform: ethyl acetate= 5:1→2:1) and concentrated in vacuo to give 2-(2-pyridylmethoxy)-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (the compound prepared in Example 67-(3)) as a colorless caramel, 338mg, which is crystallized on standing at room temperature overnight. mp 90-92°C

#### Example 97

A mixture of 2-chloro-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (prepared in Example 95) 285mg, 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine 197mg, triethylamine 0.22ml and chloroform 3ml is stirred at room temperature for 2,5 hours, followed by stirring at 60°C for 2,5 hours. The mixture is diluted with ethyl acetate, and washed with water. The water layer is extracted with ethyl acetate, and the organic layer is washed with water and an aqueous

saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue is purified with silica gel chromatography (silica gel 10g, solvent; chloroform: methanol = 50:1) and concentrated in vacuo and triturated with isopropyl ether to give 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine as a colorless crystalline powder, 290mg. mp 179-182°C, MS(m/z): 443(M+H)<sup>+</sup>

#### Example 98

2-(5,6,7,8-Tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (prepared in Example 97) 290mg and 2N aqueous sodium hydroxide solution 1.64ml are suspended in dimethyl sulfoxide-water (5ml:1ml) and stirred at room temperature for 1 hour. Tetrahydrofuran 5ml is added thereto and the mixture is stirred at room temperature for 13 hours. After removal of tetrahydrofuran in vacuo, the residue is diluted with water and neutralized with a 10% aqueous citric acid solution. The precipitate is collected, washed with water, methanol and isopropyl ether to give 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-carboxypyrimidine as a colorless crystalline powder, 187mg. mp 223-226°C(decomposition), MS(m/z): 413(M-H)<sup>-</sup>

#### Example 99-273

The corresponding starting material is treated in the same manner to prepare compounds illustrated in the following Table 5.

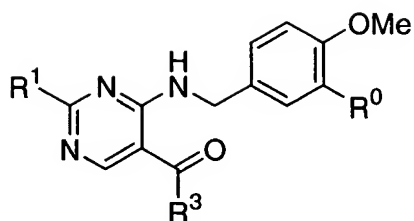


Table 5-1

Example No.	R <sup>1</sup>	R <sup>0</sup>	R <sup>3</sup>	Physical property etc.
99		Cl		mp 123-124°C
100		Cl		mp 159-162°C
101		Cl	-O-CH <sub>2</sub> CH <sub>3</sub>	mp 181.5-183°C
102		CN		mp 226-228°C
103		Cl		mp 158-160°C
104		Cl		mp 158-160°C
105		Cl		Foam MS(m/z):511(M+H) <sup>+</sup>

Table 5-2

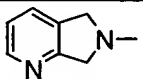
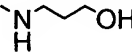
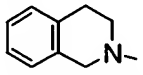
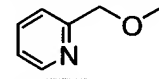
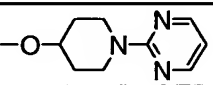
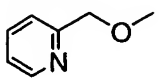
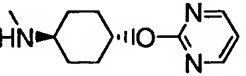
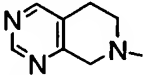
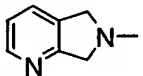
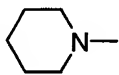
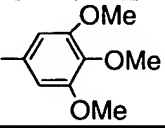
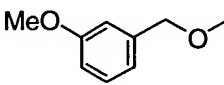
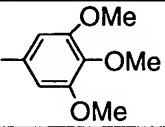
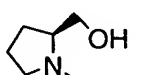
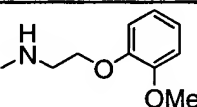
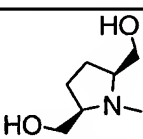
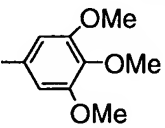
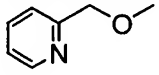
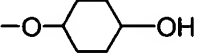
Example No.	R <sup>1</sup>	R <sup>0</sup>	R <sup>3</sup>	Physical property etc.
106		Cl		Amorphous MS(m/z):469(M+H) <sup>+</sup>
107		Cl	-O-CH <sub>2</sub> CH <sub>3</sub>	mp 122-125°C
108		Cl		Amorphous MS(m/z):562(M+H) <sup>+</sup>
109		Cl		mp 174-175°C
110		Cl	-O-CH <sub>2</sub> CH <sub>3</sub>	mp 129-133°C
111		CN	-O-CH <sub>2</sub> CH <sub>3</sub>	mp 200-203°C
112		Cl		mp 142-143°C
113		Cl		mp 122-124°C
114		Cl		Caramel MS(m/z):542(M+H) <sup>+</sup>
115		Cl		Amorphous MS(m/z):573(M+H) <sup>+</sup>
116		Cl		Amorphous MS(m/z):499(M+H) <sup>+</sup>

Table 5-3

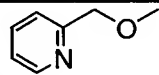
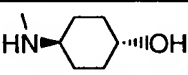
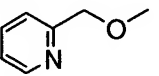
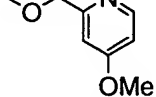
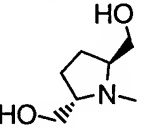
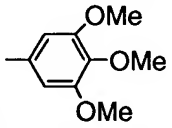
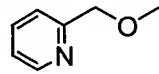
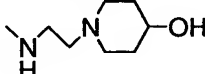
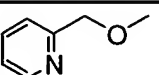
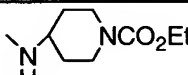
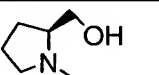
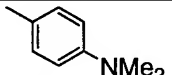
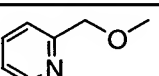
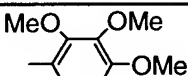
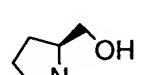
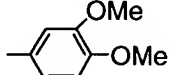
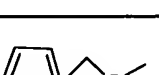
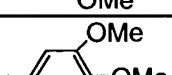
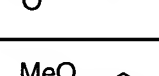
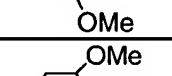
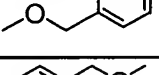
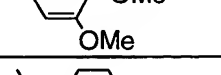
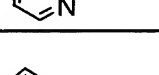
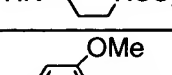
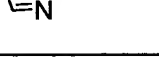
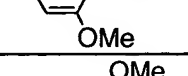
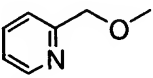
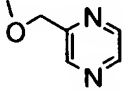
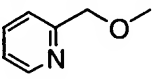
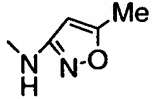
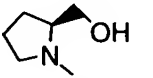
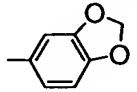
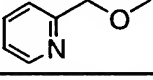
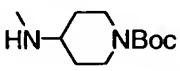
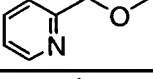
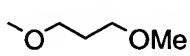
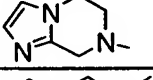
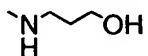
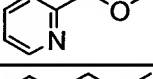
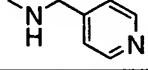
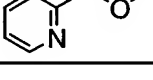
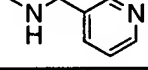
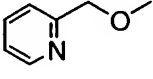
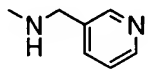
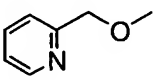
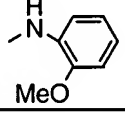
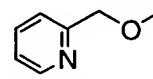
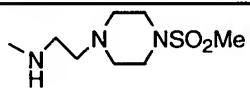
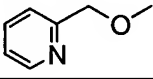
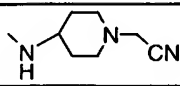
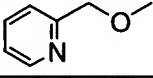
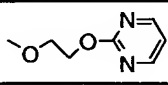
Example No.	R <sup>1</sup>	R <sup>0</sup>	R <sup>3</sup>	Physical property etc.
117		Cl		mp 139-140°C
118		Cl		mp 99-102°C
119		Cl		Amorphous MS(m/z):573(M+H) <sup>+</sup>
120		Cl		Amorphous MS(m/z):527(M+H) <sup>+</sup>
121		Cl		Amorphous MS(m/z):555(M+H) <sup>+</sup>
122		Cl		mp 92-94°C
123		CN		mp 107-108°C
124		CN		mp 171°C
125		Cl		mp 130-132°C
126		Cl		mp 122-125°C
127		Cl		mp 202-203°C
128		Cl		Amorphous MS(m/z):510(M+H) <sup>+</sup>
129		Cl		mp 140-141°C

Table 5-4

Example No.	R <sup>1</sup>	R <sup>0</sup>	R <sup>3</sup>	Physical property etc.
130		Cl		mp 118-119°C
131		Cl		Amorphous MS(m/z):481(M+H) <sup>+</sup>
132		Cl		mp 150-152°C
133*		Cl		Amorphous MS(m/z):583(M+H) <sup>+</sup>
134		Cl		mp 74-75°C
135		Cl		Amorphous MS(m/z):472(M+H) <sup>+</sup>
136		Cl		mp 160-161°C
137		Cl		mp 133-135°C
138		Cl		MsOH salt mp 98-103°C (decom.)
139		Cl		mp 123-124°C
140		Cl		Amorphous MS(m/z):590(M+H) <sup>+</sup>
141		Cl		mp 173°C
142		Cl		mp 104-109°C

\*Boc= t -butoxycarbonyl

Table 5-5

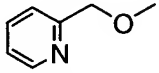
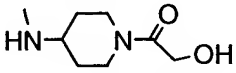
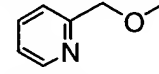
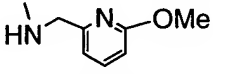
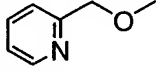
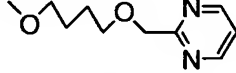
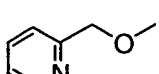
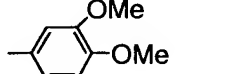
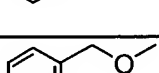
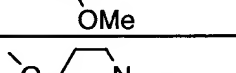
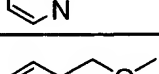
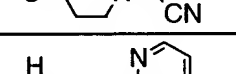
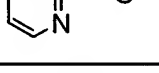
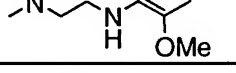
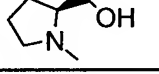
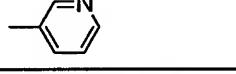
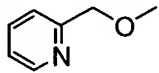
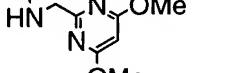
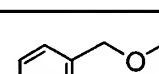
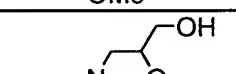
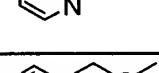
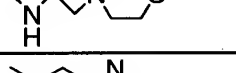
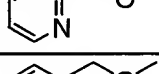
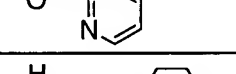
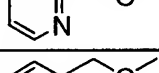
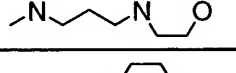
Example No.	R <sup>1</sup>	R <sup>0</sup>	R <sup>3</sup>	Physical property etc.
143		Cl		Amorphous MS(m/z):541(M+H) <sup>+</sup>
144		Cl		mp 131-134°C
145		Cl		Caramel MS(m/z):565(M+H) <sup>+</sup>
146		CN		mp 158-161°C
147		Cl		mp 109-111°C
148		Cl		mp 150-151°C
149		Cl		mp 164-165°C
150		Cl		mp 129-130°C
151		Cl		Amorphous MS(m/z):543(M+H) <sup>+</sup>
152		Cl		mp 137-139°C
153		Cl		Amorphous MS(m/z):527(M+H) <sup>+</sup>
154		Cl		mp 77-79°C
155		Cl		mp 166-167°C

Table 5-6

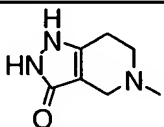
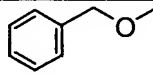
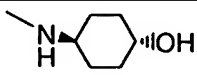
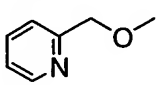
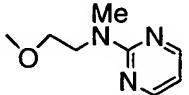
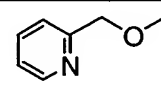
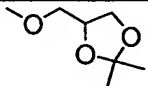
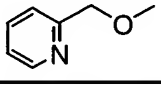
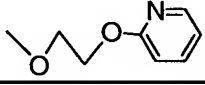
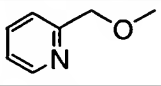
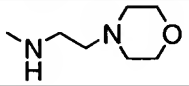
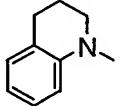
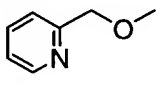
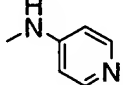
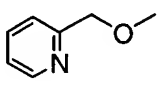
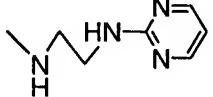
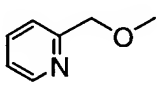
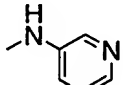
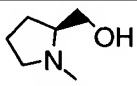

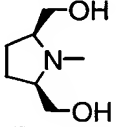
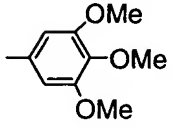
Example No.	R <sup>1</sup>	R <sup>0</sup>	R <sup>3</sup>	Physical property etc.
156		Cl	-O-CH <sub>2</sub> CH <sub>3</sub>	mp 129-132°C
157		Cl		Amorphous MS(m/z):497(M+H) <sup>+</sup>
158		Cl		mp 81-84°C
159		Cl		Oil MS(m/z):515(M+H) <sup>+</sup>
160		Cl		mp 102-103°C
161		Cl		Amorphous MS(m/z):513(M+H) <sup>+</sup>
162		Cl	-O-CH <sub>2</sub> CH <sub>3</sub>	Amorphous MS(m/z):453(M+H) <sup>+</sup>
163		Cl		mp 219-221°C
164		Cl		mp 166-167°C
165		Cl		mp 192-194°C
166		Cl		Amorphous MS(m/z):455(M+H) <sup>+</sup>
167		CN		mp 163-164°C



Table 5-7

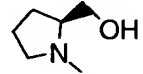
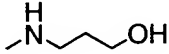
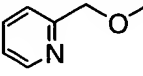
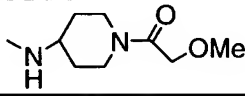
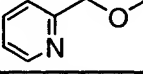
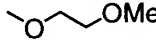
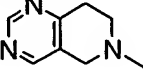
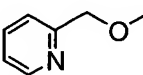
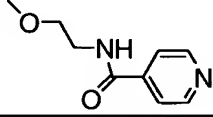
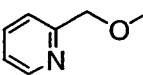
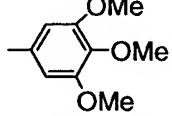
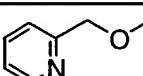
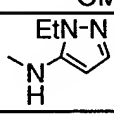
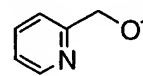
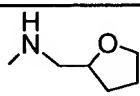
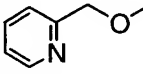
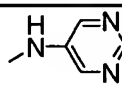
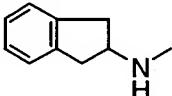
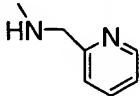
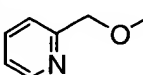
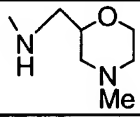
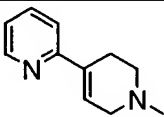
Example No.	R <sup>1</sup>	R <sup>0</sup>	R <sup>3</sup>	Physical property etc.
168		Cl		Amorphous MS(m/z):450(M+H) <sup>+</sup>
169		Cl		mp 60-65°C
170		Cl		mp 103.5-104°C
171		Cl	-O-CH <sub>2</sub> CH <sub>3</sub>	mp 166-169.5°C
172		Cl		Amorphous MS(m/z):549(M+H) <sup>+</sup>
173		F		mp 118-121°C
174		Cl		Amorphous MS(m/z):494(M+H) <sup>+</sup>
175		Cl		mp 116-117°C
176		Cl		mp 210-212°C
177		Cl		mp 184-184.5°C
178		Cl		Amorphous MS(m/z):513(M+H) <sup>+</sup>
179		Cl	-O-CH <sub>2</sub> CH <sub>3</sub>	mp 132-134°C

Table 5-8

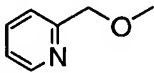
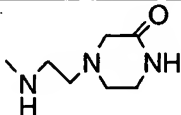
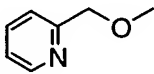
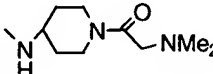
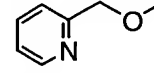
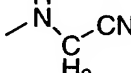
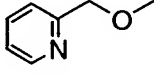
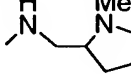
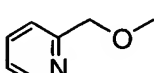
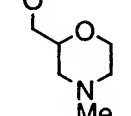
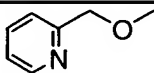
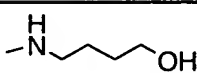
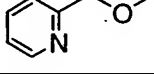
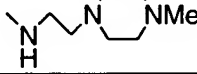
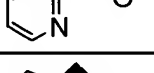
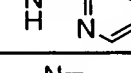
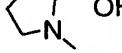


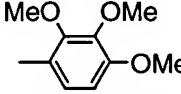
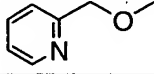
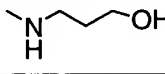
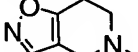
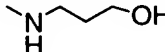
Example No.	R <sup>1</sup>	R <sup>0</sup>	R <sup>3</sup>	Physical property etc.
180		Cl		Amorphous MS(m/z):526(M+H) <sup>+</sup>
181		Cl		Amorphous MS(m/z):568(M+H) <sup>+</sup>
182		Cl		mp 166-168°C
183		Cl		Amorphous MS(m/z):497(M+H) <sup>+</sup>
184		Cl		Amorphous MS(m/z):514(M+H) <sup>+</sup>
185		Cl		mp 124-125°C
186		Cl		mp 96 - 98°C
187		Cl		mp 133-136°C
188		Cl		Amorphous MS(m/z):454(M+H) <sup>+</sup>
189		CN		mp 82-85°C
190		Cl		mp 155-156°C
191		Cl		Amorphous MS(m/z):473(M+H) <sup>+</sup>

Table 5-9

Example No.	R <sup>1</sup>	R <sup>0</sup>	R <sup>3</sup>	Physical property etc.
192		Cl	-O-CH <sub>2</sub> CH <sub>3</sub>	mp 220-223°C
193		Cl		Amorphous MS(m/z):538(M+H) <sup>+</sup>
194		Cl		mp 146-147°C
195		NO <sub>2</sub>		Amorphous MS(m/z):509(M+H) <sup>+</sup>
196		Cl		mp 124-126°C
197		Cl		mp 158-159°C
198		Cl	-O-CH <sub>2</sub> CH <sub>3</sub>	mp 280-282°C
199		CN		mp 176-177°C
200		Cl		mp 174-175°C
201		Cl		mp 144-147°C
202		Cl		mp 110-112°C

Table 5-10

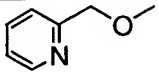
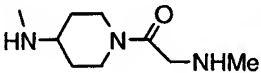
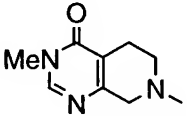
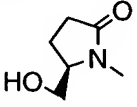
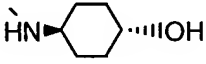
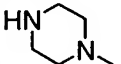
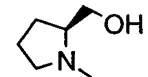
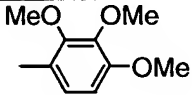
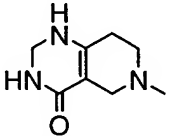
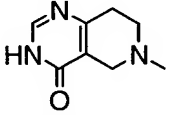
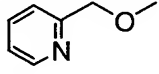
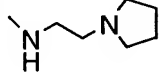
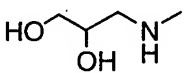
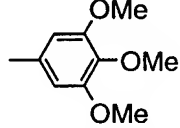
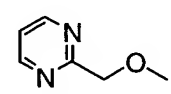
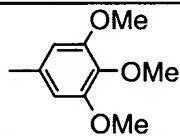
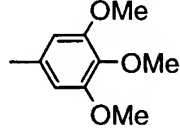
Example No.	R <sup>1</sup>	R <sup>0</sup>	R <sup>3</sup>	Physical property etc.
203		Cl		Amorphous MS(m/z):554(M+H) <sup>+</sup>
204		Cl	-O-CH <sub>2</sub> CH <sub>3</sub>	mp 217-220°C
205		Cl		Amorphous MS(m/z):504(M+H) <sup>+</sup>
206		Cl	-O-CH <sub>2</sub> CH <sub>3</sub>	mp 123-124.5°C
207		CN		mp 130-132°C
208		Cl	-O-CH <sub>2</sub> CH <sub>3</sub>	mp 139-142°C
209		Cl	-O-CH <sub>2</sub> CH <sub>3</sub>	mp 236-239°C
210		Cl		Amorphous MS(m/z):497(M+H) <sup>+</sup>
211		Cl		Powder(HCl) MS(m/z):533(M+H) <sup>+</sup>
212		CN		mp 175-176°C
213	MeO-	CH <sub>2</sub> O H		mp 158-161°C

Table 5-11

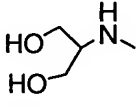
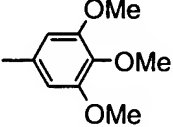
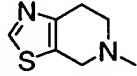
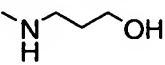
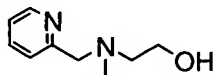
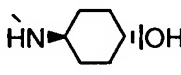
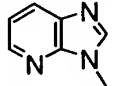
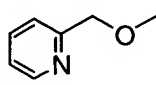
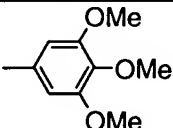
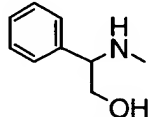
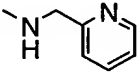
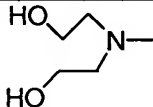
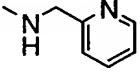
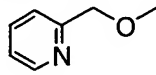
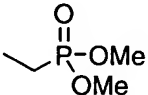
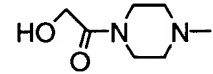
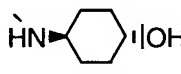
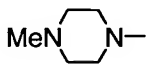
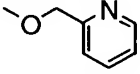
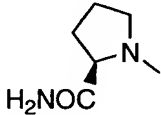
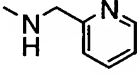
Example No.	R <sup>1</sup>	R <sup>0</sup>	R <sup>3</sup>	Physical property etc.
214		Cl		Powder(HCl) MS(m/z):533(M+H) <sup>+</sup>
215		Cl		Amorphous MS(m/z):489(M+H) <sup>+</sup>
216		Cl		Amorphous MS(m/z):541(M+H) <sup>+</sup>
217		Cl	-O-CH <sub>2</sub> CH <sub>3</sub>	mp 118-220°C
218		NHCH O		mp 171-173°C
219		Cl		Amorphous MS(m/z):519(M+H) <sup>+</sup>
220		Cl		Powder(HCl) MS(m/z):487(M+H) <sup>+</sup>
221		Cl		Oil MS(m/z):507(M+H) <sup>+</sup>
222		Cl		Amorphous MS(m/z):535(M+H) <sup>+</sup>
223		Cl		mp 146-147°C
224		Cl		Amorphous MS(m/z):496(M+H) <sup>+</sup>

Table 5-12

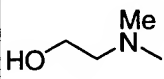
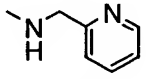
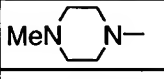
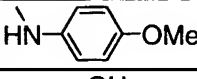
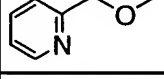
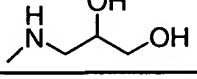
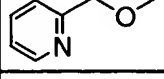
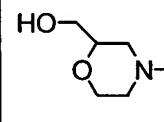
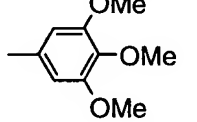
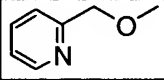

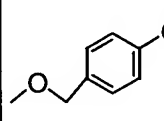
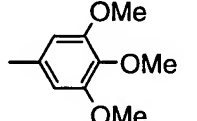
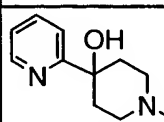
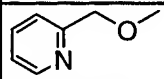
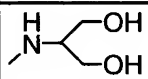
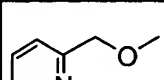
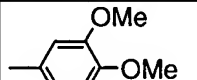
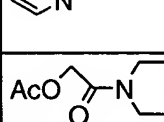
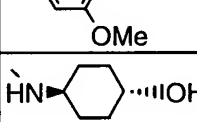
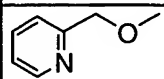
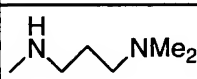
Example No.	R <sup>1</sup>	R <sup>0</sup>	R <sup>3</sup>	Physical property etc.
225		Cl		mp 217-219°C
226		Cl		mp 162-163°C
227		Cl		mp 153-155°C
228		Cl	-NMe <sub>2</sub>	mp 129-130°C
229		CN		mp 186-188°C
230		Cl		mp 164-165°C
231		Cl		mp 114-119°C
232		Cl	-O-CH <sub>2</sub> CH <sub>3</sub>	Amorphous MS(m/z):498(M+H) <sup>+</sup>
233		Cl		mp 175-176°C
234		CH <sub>2</sub> O-Ac		Amorphous MS(m/z):589(M+H) <sup>+</sup>
235		Cl		Amorphous MS(m/z):575(M+H) <sup>+</sup>
236		Cl		mp 84-86°C

Table 5-13

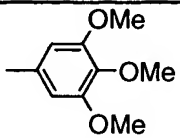
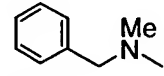
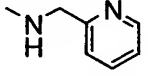
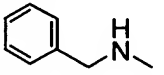
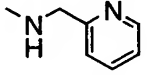
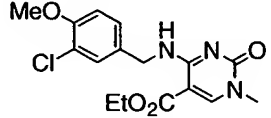
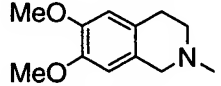
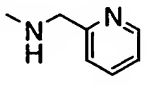

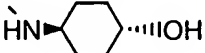
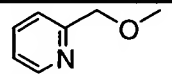
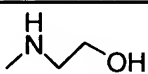
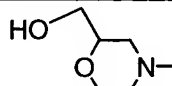
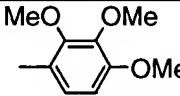
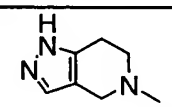
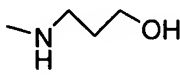
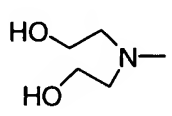
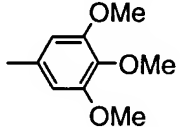
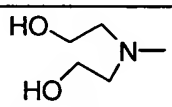
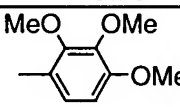
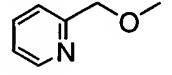
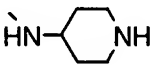
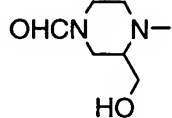
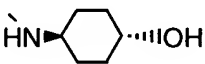
Example No.	R <sup>1</sup>	R <sup>0</sup>	R <sup>3</sup>	Physical property etc.
237	EtO-	CN		mp 165°C
238		Cl		mp 132-134°C
239		Cl		mp 195-197°C
240		Cl	-O-CH <sub>2</sub> CH <sub>3</sub>	mp 105-108°C
241		Cl		Powder(HCl) MS(m/z):575(M+H) <sup>+</sup>
242		Cl		mp 158-159°C
243		Cl		mp 162-163°C
244		CN		mp 104-108°C
245		Cl		mp 113-117°C
246		CN		mp 165-167°C
247		CN		mp 108-110°C
248		Cl		mp 119-121°C
249		Cl		Amorphous

Table 5-14

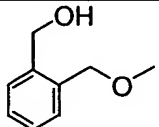
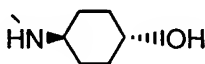
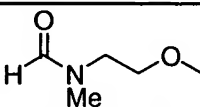
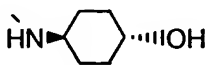
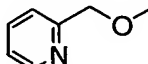
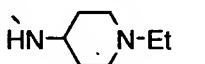
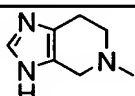
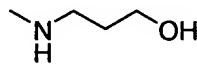
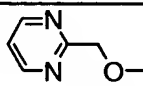
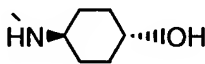
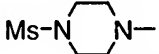
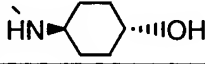
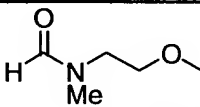
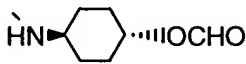
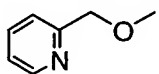
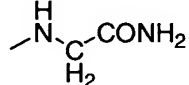
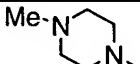
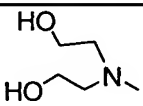
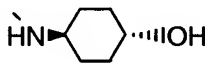
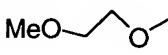

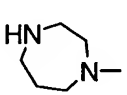
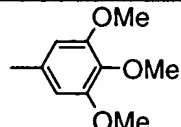
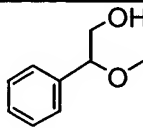
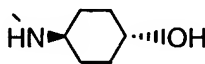
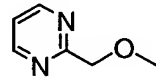
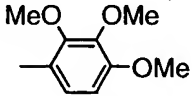
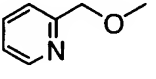
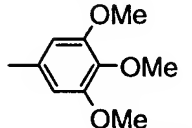
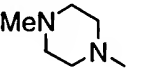
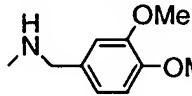

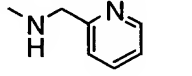
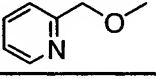
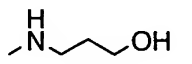
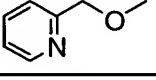
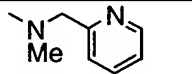
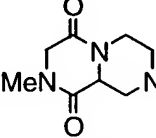
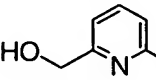
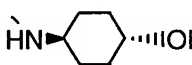
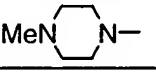
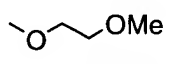
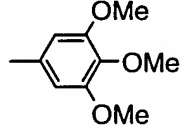
Example No.	R <sup>1</sup>	R <sup>0</sup>	R <sup>3</sup>	Physical property etc.
250		Cl		mp 115-120°C
251		Cl		Amorphous MS(m/z):492(M+H) <sup>+</sup>
252		Cl		mp 124-126°C
253		Cl		Amorphous MS(m/z):472(M+H) <sup>+</sup>
254		Cl		mp 135-137°C
255		Cl		mp 158-161°C
256		Cl		Amorphous MS(m/z):520(M+H) <sup>+</sup>
257		Cl		mp 187-188°C
258		Cl	-O-CH <sub>2</sub> CH <sub>3</sub>	mp 136.5-137°C
259		Cl		mp 149-151°C
260		Cl		mp 170-172°C
261		Cl		Powder(HCl) MS(m/z):542(M+H) <sup>+</sup>
262		Cl		Amorphous MS(m/z):527(M+H) <sup>+</sup>



Table 5-15

Example No.	R <sup>1</sup>	R <sup>0</sup>	R <sup>3</sup>	Physical property etc.
263		CN		mp 164-166°C
264		SOMe		Amorphous MS(m/z):579(M+H) <sup>+</sup>
265		Cl		Amorphous MS(m/z):541(M+H) <sup>+</sup>
266	Me <sub>2</sub> N-	Cl		mp 87-89°C
267	Me <sub>2</sub> N-	Cl		mp 162-163°C
268		NO <sub>2</sub>		mp 173-176°C
269		Cl		Amorphous MS(m/z):505(M+H) <sup>+</sup>
270		Cl	-O-CH <sub>2</sub> CH <sub>3</sub>	mp 165-167°C
271		Cl		Oil MS(m/z):528(M+H) <sup>+</sup>
272		Cl		mp 112.5-113°C
273	MeO-	CN		mp 174-175°C

Example 274-286

The corresponding starting material is treated in the same manner to prepare compounds illustrated in the following Table 6.

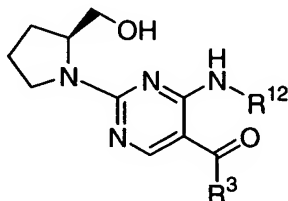
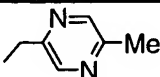
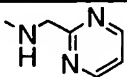
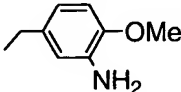
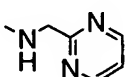
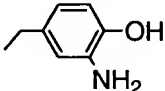
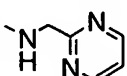
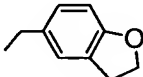
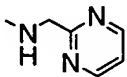
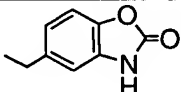
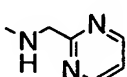
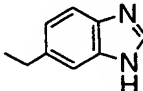
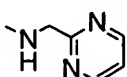


Table 6-1

Example No.	R <sup>12</sup>	R <sup>3</sup>	Physical property etc.
274		-OEt	mp 92.5-93.5°C
275			Powder MS(m/z):480(M+H) <sup>+</sup>
276			Powder MS(m/z):470(M+H) <sup>+</sup>
277			Powder MS(m/z):484(M+H) <sup>+</sup>
278			Powder MS(m/z):460(M+H) <sup>+</sup>
279			Powder MS(m/z):454(M+H) <sup>+</sup>
280			Amorphous MS(m/z):512(M+H) <sup>+</sup>

Table 6-2

Example No.	R <sup>12</sup>	R <sup>3</sup>	Physical property etc.
281			Powder MS(m/z):436(M+H) <sup>+</sup>
282			Powder MS(m/z):465(M+H) <sup>+</sup>
283			Powder MS(m/z):451(M+H) <sup>+</sup>
284			Powder MS(m/z):462(M+H) <sup>+</sup>
285			Powder MS(m/z):475(M+H) <sup>+</sup>
286			Powder MS(m/z):460(M+H) <sup>+</sup>

## Example 287

(1) 98% Formic acid 1.44ml is dropped to acetic anhydride 2.86ml under ice cooling and the mixture is stirred at 60°C for 1 hour. After ice cooling the reaction mixture is diluted with tetrahydrofuran 15ml, and thereto is added under ice cooling a solution of 3-chloro-4-methoxybenzylamine 2.00g in tetrahydrofuran 16ml. The reaction mixture is stirred at room temperature for 1 hour.

Tetrahydrofuran is removed in vacuo at 35°C and the residue is made alkaline with an aqueous saturated sodium hydrogen carbonate solution. The mixture is extracted twice with ethyl acetate and the combined organic layer is washed with water and an aqueous saturated sodium hydrogen carbonate solution, dried over sodium sulfate and concentrated in vacuo. The residue is separated with silica gel chromatography (silica gel 30g, solvent; chloroform: ethyl acetate = 1:1) and

concentrated in vacuo to give a compound as a colorless crystalline powder 2.05g. mp 82-85°C, MS(m/z): 200(M+H)<sup>+</sup>

(2) To a solution of the compound (prepared in the above (1)) 2.02g in tetrahydrofuran 38ml is dropped 10M boron-methyl sulfide complex(BH<sub>3</sub>·Me<sub>2</sub>S) 4.55ml over a period of 5 minutes under ice cooling. The mixture is stirred on an ice bath for 30 minutes and then refluxed for 2 hours. After ice cooling methanol 10ml is dropped thereto and the reaction mixture is stirred at room temperature for 30 minutes. To the mixture is added 4.9N hydrochloric acid in methanol 20ml and the mixture is refluxed for 30 minutes. The solvent is removed in vacuo and the residue is diluted with water and the mixture is washed with isopropyl ether-ethyl acetate (1:1) and the organic layer is extracted with 10% hydrochloric acid. The combined water layer is washed with isopropyl ether-ethyl acetate (2:1), is made alkaline with a 10% aqueous sodium hydroxide solution and the solution is extracted twice with ethyl acetate. The combined organic layer is washed with a 10% aqueous sodium hydroxide solution, water, and an aqueous saturated sodium chloride solution, dried over sodium sulfate and concentrated in vacuo to give N-methyl-(3-chloro-4-methoxy)benzylamine 1.62g as a pale brown oil. MS(m/z): 186(M+H)<sup>+</sup>

(3) A mixture of 2,4-dichloro-5-(3,4,5-trimethoxyphenylcarbonyl)pyrimidine 120mg, the compound (prepared in the above (2)) 68mg, triethylamine 37mg and anhydrous dimethylformamide 3ml is stirred for 1 hour under ice cooling and is diluted with a 10% aqueous citric acid solution. The solution is extracted twice with ethyl acetate and the combined organic layer is washed with water and an aqueous saturated sodium chloride solution, dried over sodium sulfate and concentrated in vacuo. The residue is separated with silica gel chromatography (silica gel 10g, solvent; chloroform: ethyl acetate = 100:1→50:1).

The first fraction is concentrated in vacuo and crystallized from a mixture of diisopropyl ether and hexane to give 4-chloro-5-(3,4,5-trimethoxyphenylcarbonyl)-2-[N-methyl-N-(3-chloro-4-methoxybenzyl)amino]pyrimidine as a colorless crystalline powder 30mg. mp 103-104°C, MS(m/z): 492(M+H)<sup>+</sup>

The second fraction is concentrated in vacuo to give 2-chloro-5-(3,4,5-trimethoxyphenylcarbonyl)-4-[N-methyl-N-(3-chloro-4-methoxybenzyl)amino]pyrimidine as a colorless foam 109mg. MS(m/z): 492(M+H)<sup>+</sup>

(4) 2-Chloro-5-(3,4,5-trimethoxyphenylcarbonyl)-4-[N-methyl-N-(3-chloro-4-methoxybenzyl)amino]pyrimidine (prepared in the above (3)) is treated in the same manner as Example 1-(4) to give 2-(2-pyridylmethoxy)-5-(3,4,5-trimethoxyphenylcarbonyl)-4-[N-methyl-N-(3-chloro-4-methoxybenzyl)amino]pyrimidine as a colorless crystalline powder 74mg. mp 154-157°C, MS(m/z): 565(M+H)<sup>+</sup>

#### Examples 288-290

The corresponding starting compounds are treated in the same manner as Example 287 to give the compounds listed in the following Table 7.

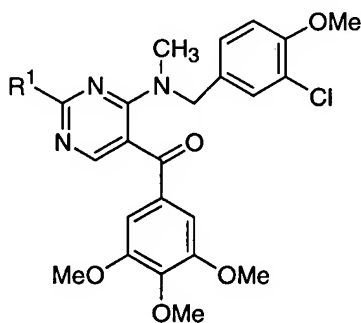
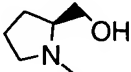
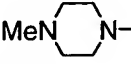
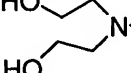


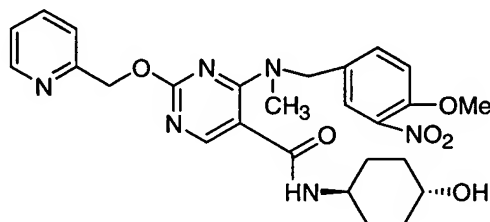
Table 7

Example No.	R <sup>1</sup>	Physical property etc.
-------------	----------------	------------------------

288		Powder(HCl) MS(m/z):557(M+H) <sup>+</sup>
289		Powder(HCl) MS(m/z):556(M+H) <sup>+</sup>
290		Powder(HCl) MS(m/z):561(M+H) <sup>+</sup>

#### Example 291

The following compounds are prepared in the same manner from the corresponding starting compounds.



mp 169-171°C

#### Examples 292-296

The following compounds are prepared in the same manner from the corresponding starting compounds.

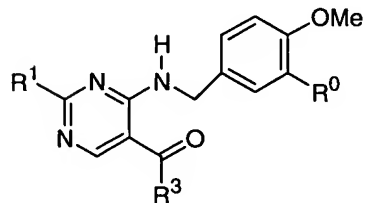
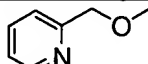
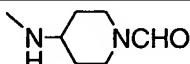


Table 8

Example No.	R <sup>1</sup>	R <sup>0</sup>	R <sup>3</sup>	Physical property etc.
292		Cl		mp 181-183°C

293		Cl		Oil MS(m/z):503(M+H) <sup>+</sup>
294		Cl		mp 143-145°C
295		Cl		mp 111-113°C
296		CN	-OEt	Amorphous MS(m/z):412(M+H) <sup>+</sup>

### Example 297

(1) To a solution of diisopropylamine (0.78g) in tetrahydrofuran (40ml) is dropped a 1.6M solution of n-butyl lithium in hexane (4.82ml) over a period of 3 minutes under cooling on dry ice in acetone bath. The mixture is stirred on the same bath for 30 minutes and thereto is added 2,6-dichloropyrazine 0.50g in tetrahydrofuran 5ml at the same temperature over a period of 15 minutes. After stirring for 1 hour, the mixture is poured into dry ice and stirred at room temperature for 1 hour. The mixture is diluted with 10% hydrochloric acid to be adjusted pH about 2 and extracted with ethyl acetate. The combined organic layer is extracted with an aqueous saturated sodium hydrogen carbonate solution. The water extract is washed with ethyl acetate and made acid with a 10% aqueous hydrochloric acid solution and extracted with ethyl acetate. The combined organic layer is washed with water and an aqueous saturated sodium chloride solution, dried over sodium sulfate and concentrated in vacuo. The residue is triturated with chloroform-hexane (1:1) to give 2-carboxy-3,5-dichloropyrazine 234mg as a slightly brownish crystalline powder. mp 139-141°C, MS(m/z): 191(M-H)<sup>-</sup>

(2) A mixture of 2-carboxy-3,5-dichloropyrazine (prepared in the above (1)) 226mg, sodium hydrogen carbonate 118mg, methyl iodide 0.5ml and dimethylformamide 1.8ml is stirred at room temperature for 14 hours. The mixture is

diluted with a 10% aqueous citric acid solution and extracted with ethyl acetate. The combined organic layer is washed with water and an aqueous saturated sodium chloride solution, dried over sodium sulfate and concentrated in vacuo to give 2-methoxycarbonyl-3,5-dichloropyrazine as a pale brown crystalline powder 245mg. mp 60-63°C, MS(m/z): 206(M<sup>+</sup>)

(3) A mixture of 2-methoxycarboxy-3,5-dichloropyrazine (prepared in the above (2)) 234mg, 3-chloro-4-methoxybenzylamine 204mg, triethylamine 0.17ml and anhydrous toluene 3ml is stirred for 7 hours at room temperature. The reaction mixture is diluted with a 10% aqueous citric acid solution and the solution is extracted with ethyl acetate. The extract is washed with water and an aqueous saturated sodium chloride solution, dried over sodium sulfate and concentrated in vacuo. The residue is purified and separated with silica gel chromatography (silica gel 5mg, solvent; hexane: chloroform = 1:1) and then the desired fraction is concentrated in vacuo to give 2-methoxycarbonyl-3-(3-chloro-4-methoxybenzylamino)-5-chloropyrazine as a pale yellow crystalline powder 102mg. mp 149-151°C, MS(m/z): 342(M+H)<sup>+</sup>

#### Example 298

To a mixture of 2-methoxycarbonyl-3-(3-chloro-4-methoxybenzylamino)-5-chloropyrazine (prepared in the above Example 297(3)) 71mg and 2-hydroxymethylpyridine 25mg in tetrahydrofuran 3ml is added potassium tert-butoxide 26mg under ice cooling. The mixture is stirred for 30 minutes at the same temperature and diluted a 10% aqueous citric acid solution. The solution is extracted with ethyl acetate and the extract is washed with water and an aqueous saturated sodium chloride solution, dried over sodium sulfate and concentrated in vacuo. The residue is purified and separated with silica gel chromatography (silica gel 5g, solvent; chloroform: ethyl



acetate = 3:1) and crystallized from isopropyl ether to give 2-methoxycarbonyl-3-(3-chloro-4-methoxybenzylamino)-5-(2-pyridylmethoxy)pyrazine as a pale yellow crystalline powder, 25mg. mp 132-133°C, MS(m/z): 415(M+H)<sup>+</sup>

#### Example 299

A mixture of 2-methoxycarbonyl-3-(3-chloro-4-methoxybenzylamino)-5-chloropyrazine (prepared in 297-(3)) 150mg, 2-hydroxymethylpyrrolidine 88.6mg and triethylamine 0.12ml in tetrahydrofuran 5ml is stirred for 4 hours at room temperature and heated at 50°C for 2 hours. Then 2-hydroxymethylpyrrolidine 44.3mg is added thereto and the mixture is heated at 50°C for 1 hour. After cooling, water is added thereto and the solution is extracted with ethyl acetate. The extract is washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The resulting yellowish oil is purified with silica gel flash column chromatography (solvent; chloroform: hexane = 1:1) to give (S)-2-methoxycarbonyl-3-(3-chloro-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl)pyrazine as a pale yellowish powder, 123mg. MS(m/z): 407(M+H)<sup>+</sup>

#### Example 300

A compound listed in Table 9 is prepared from a corresponding starting compound in the same manner as described above.

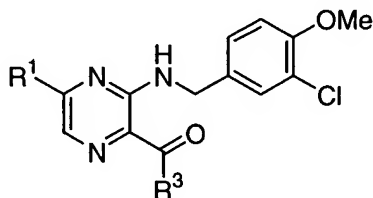
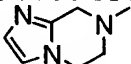


Table 9

Example No.	R <sup>1</sup>	R <sup>3</sup>	Physical property etc.
300		-OMe	Amorphous MS(m/z):429(M+H) <sup>+</sup>

## Example 301

(1) A mixture of 5-benzoyloxy-2-(3,4,5-trimethoxybenzoyl)benzoic acid 50mg, 14.8M aqueous ammonia 50μl, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimido · hydrochloride 68mg and 1-hydroxybenzotriazole 15.9mg is dissolved under ice cooling in N,N-dimethylformamide 2ml and the mixture is stirred overnight at room temperature. To the reaction mixture is added water. The mixture is extracted with ethyl acetate and the extract is washed with water and dried, followed by removal of the solvent. The residue is purified with silica gel chromatography (solvent: chloroform: ethyl acetate=1:1) and left to be crystallized. The crystals are triturated with diisopropyl ether-ethyl acetate to give 6-benzyloxy-3-hydroxy-3-(3,4,5-trimethoxyphenyl)-2,3-dihydroisoindol-1-one 46.7mg. mp 187-189°C

(2) To a suspension of the compound (prepared in the above (1)) 1.065g in dioxane 20ml is added at room temperature 2M aqueous sodium hydroxide solution 10.11 ml. Thereto is added at room temperature a 9% aqueous sodium hypobromite (NaOBr) solution 12.4ml, and the mixture is stirred overnight. To the mixture is added an aqueous sodium hydrogen carbonate solution and the mixture is extracted with ethyl acetate. The extract is washed, dried and the solvent is removed. The residue is purified with silica gel chromatography (solvent: hexane: ethyl acetate=1:1) and crystallized from diisopropyl ether-ethyl acetate to give 5-benzyloxy-2-(3,4,5-trimethoxybenzoyl)aniline 0.662mg. mp 79-80°C

(3) To a solution of the compound (prepared in the above (2)) 1g in methanol 30ml is added palladium-carbon 100mg, and the mixture is stirred for 3 hours under hydrogen atmosphere (1 atm.). After removal of catalyst the filtrate is concentrated to give 5-hydroxy-2-(3,4,5-trimethoxybenzoyl)aniline 847mg as an amorphous.

(4) To a mixture of the compound (prepared in the above (3)) 300mg and 2-picolyl chloride hydrochloride 78mg in N,N-dimethylformamide 5ml is added under ice cooling 60% sodium hydride 103mg, and the mixture is stirred for 1 hour. The reaction mixture is poured into water, extracted with ethyl acetate and the extract is washed with water, dried and removed the solvent. The residue is purified with silica gel chromatography (solvent: chloroform: methanol = 80:1) to give 5-(2-pyridylmethoxy)-2-(3,4,5-trimethoxybenzoyl)aniline as an amorphous 238mg.

(5) A mixture of the compound (prepared in the above (4)) 100mg, 3-chloro-4-methoxybenzyl chloride 53mg, 60% sodium hydride and tetrahydrofuran 4ml is refluxed under heating for 24 hours. After reaction mixture is cooled and poured into water, the solution is extracted with ethyl acetate. The extract is washed with brine, dried over aqueous sodium sulfate and concentrated in vacuo. The residue is purified with silica gel chromatography (solvent; chloroform: ethyl acetate = 20:1) and triturated with methanol to give 1-(2-pyridylmethoxy)-3-(3-chloro-4-methoxybenzylamino)-4-(3,4,5-trimethoxybenzoyl)benzene 21mg as yellow crystals. mp 142-144°C, MS(m/z): 549(M+H)<sup>+</sup>

#### Example 302

(1) A mixture of 4-chloro-2-nitrobenzoic acid methyl ester 100mg, prolinol 235mg and 1-methyl-2-pyrrolidinone 3ml is stirred at 100°C for 3 hours. After cooling to room temperature, ethyl acetate and water are added to the mixture. The organic layer is

washed with water (twice) and brine, and dried over sodium sulfate. After removal of the sodium sulfate, the filtrate is concentrated in vacuo, and the residue is purified with preparative thin-layer chromatography (two plates, solvent; hexane: ethyl acetate=1:1) to give 4-(2-hydroxymethyl-1-pyrrolidiny)-2-nitrobenzoic acid methyl ester 20mg as a yellow oil. MS(m/z): 281(M+H)<sup>+</sup>

(2) A mixture of 4-chloro-2-nitrobenzoic acid methyl ester 100mg, prolinol 56mg, diisopropylethylamine 90mg and 1-methyl-2-pyrrolidinone 3ml is stirred at 100°C for 13 hours. Ethyl acetate and water are added to the mixture, and the organic layer is washed with water (twice) and brine, and dried over sodium sulfate. After removal of the sodium sulfate, the filtrate is concentrated in vacuo, and the residue is purified with column chromatography (silica gel 100g, solvent; hexane: ethyl acetate=4:1→2:1→1:1→100% ethyl acetate) to give 4-(2-hydroxymethyl-1-pyrrolidiny)-2-nitrobenzoic acid methyl ester 1.298g as a pale yellow viscosity oil. MS(m/z): 285(M+H)<sup>+</sup>

(3) A mixture of the compound (prepared in the above (1) or (2)) 260mg, 10% palladium-carbon 25mg and ethanol 10ml is subjected to hydrogenation under hydrogen atmosphere at room temperature for 7 hours. After removal of catalyst by filtration the filtrate is concentrated in vacuo. The residue is purified with column chromatography (NH-silica gel 25g, solvent; hexane: ethyl acetate = 1:1→ ethyl acetate) to give 4-(2-hydroxymethyl-1-pyrrolidiny)-2-aminobenzoic acid methyl ester as pale yellow crystals, 185mg. mp 113-115°C, MS(m/z): 251(M+H)<sup>+</sup>

(4) To a mixture of the compound (prepared in the above (3)) 50mg, 3-chloro-4-methoxybenzaldehyde 61mg, acetic acid 21mg and 1,2-dichloroethane 2ml is added at room temperature triacetoxy sodium hydrogen borate 113mg. The mixture is stirred for 1 hour and thereto are added ethyl acetate and an aqueous saturated sodium hydrogen

carbonate solution. The organic layer is washed with water and brine, and dried over sodium sulfate. After removal of sodium sulfate by filtration the filtrate is concentrated in vacuo. The residue is purified with preparative thin-layer chromatography (2 sheets, solvent; hexane: ethyl acetate=1:1) to give a red amorphous compound. The compound is further purified with preparative thin-layer chromatography (2 sheets, solvent; chloroform: methanol = 20:1) to give 4-(2-hydroxymethyl-1-pyrrolidinyl)-2-(3-chloro-4-methoxybenzylamino)benzoic acid methyl ester as a red powder, 75mg. MS(m/z): 405(M+H)<sup>+</sup>

(5) A mixture of the compound (prepared in the above (4)) 459mg, a 10% aqueous sodium hydroxide solution 2ml and dimethyl sulfoxide 4ml are stirred at room temperature for 4 days. To the mixture are added ethyl acetate and water and then the mixture is neutralized with 10% hydrochloric acid. The organic layer is washed with water (three times) and brine, and dried over sodium sulfate. After removal of sodium sulfate by filtration the filtrate is concentrated in vacuo. The residue is purified with chromatography (silica gel 40g, solvent; chloroform: methanol = 100:3, and then silica gel 40g, solvent; hexane: ethyl acetate = 1:1) and the desired fraction is triturated with diethyl ether to give 4-(2-hydroxymethyl-1-pyrrolidinyl)-2-(3-chloro-4-methoxybenzylamino)benzoic acid 255mg. mp 132-134°C (decomposition), MS(m/z): 391(M+H)<sup>+</sup>

(6) A mixture of the compound (prepared in the above (5)) 80mg, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimido·hydrochloride 59mg, 1-hydroxybenzotriazole 42mg, 2-aminomethylpyrimidine 34mg and dimethylformamide 3ml are stirred at room temperature for a day. To the mixture are added 2-aminomethylpyrimidine 68mg and the mixture is stirred at room temperature for 3 days. Ethyl acetate and an aqueous saturated sodium hydrogen carbonate solution are added thereto and the organic layer

is washed with water (five times) and brine, and dried over sodium sulfate. After removal of sodium sulfate by filtration the filtrate is concentrated in vacuo. The residue is purified with preparative thin-layer chromatography (2 sheets, solvent; ethyl acetate) to give pale yellow crystals and the crystals are triturated with a mixture of ethyl acetate and diethyl ether to give 4-(2-hydroxymethyl-1-pyrrolidinyl)-2-(3-chloro-4-methoxybenzylamino)-N-(2-pyrimidinylmethyl)benzamide 37mg. mp 102-107°C, MS(m/z): 482(M+H)<sup>+</sup>

### Example 303

A compound listed in the following Table 10 is prepared by treating a corresponding starting compound in the same manner as Example 302.

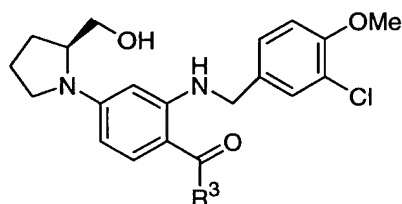


Table 10

Example No.	R <sup>3</sup>	Physical property etc.
303		Amorphous MS(m/z):503(M+H <sup>+</sup> )

### Example 304

(1) A mixture of 4,6-dihydroxynicotinic acid ethyl ester 7.80g and phosphoryl chloride 48ml is stirred for 8 hours at 100°C. The excess phosphoryl chloride is removed in vacuo and the residue is poured into ice water. The mixture is made basic with sodium carbonate and extracted with ethyl acetate. The extract is washed with

water and brine, and dried over sodium sulfate. After removal of the sodium sulfate, the filtrate is concentrated in vacuo, and the residue is purified with column chromatography (silica gel 100g, solvent; hexane: ethyl acetate=10:1) to give 4, 6-dichloronicotinic acid ethyl ester 8.50g as colorless crystals. mp 32-32.5°C, MS(m/z): 220(M+H)<sup>+</sup>

(2) A mixture of the compound (prepared in the above (1)) 1.02g, 3-chloro-4-methoxybenzylamine 1.02g, triethylamine 823mg and acetonitrile 20ml is stirred at room temperature for 1.5 days and then refluxed for 3 hours. After removal of the solvent the residue is diluted with a mixture of ethyl acetate and an aqueous sodium hydrogen carbonate solution. The organic layer is washed with an aqueous saturated sodium hydrogen carbonate solution, water and brine, and dried over sodium sulfate. After removal of the sodium sulfate, the filtrate is concentrated in vacuo, and the residue is purified with column chromatography (silica gel 25g, solvent; hexane: ethyl acetate=4:1) and triturated with cooled diethyl ether to give 2-chloro-4-(3-chloro-4-methoxybenzylamino)nicotinic acid ethyl ester 1.17g as colorless crystals. mp 115.5-117.5°C, MS(m/z): 355(M+H)<sup>+</sup>

(3) A mixture of the compound (prepared in the above (2)) 500mg, a 10% aqueous sodium hydroxide solution 5ml and dimethyl sulfoxide 20ml is stirred for 15 hours at room temperature. The mixture is acidified (pH about 5) with a 10% aqueous hydrochloric acid solution at 0°C. After dropping water thereto, the mixture is stirred at room temperature for 1 hour and the precipitate is filtered and the filtrate is washed with water and concentrated in vacuo to give 2-chloro-4-(3-chloro-4-methoxybenzylamino)nicotinic acid 441mg. mp 228-230°C, MS(m/z): 325(M-H)<sup>-</sup>

(4) A mixture of the compound (prepared in the above (3)) 100mg, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide · hydrochloride 88mg, 1-hydroxybenzotriazole 62mg, 2-aminomethylpyrimidine 50mg and dimethylformamide

3ml is stirred for 1 day at room temperature. To the mixture are added ethyl acetate and an aqueous sodium hydrogen carbonate solution, and the organic layer is washed with water (four times) and brine and dried over sodium sulfate. After removal of the sodium sulfate, the filtrate is concentrated in vacuo, and the residue is triturated with diethyl ether to give 3-(2-pyrimidinylmethylaminocarbonyl)-6-chloro-4-(3-chloro-4-methoxybenzylamino)pyridine 76mg as colorless crystals. mp 133.5-136.5°C, MS(m/z): 418(M+H)<sup>+</sup>

(5) A mixture of the compound (prepared in the above (4)) 66mg, prolinol 80mg and 1-methyl-2-pyrrolidinone 3ml is stirred at 200°C for 4.5 hours. After the mixture is cooled to room temperature, ethyl acetate and an aqueous sodium hydrogen carbonate solution are added to the mixture and the organic layer is washed with water (five times) and brine, and dried over sodium sulfate. After removal of the sodium sulfate, the filtrate is concentrated in vacuo, and the residue is purified with preparative thin-layer chromatography (3 sheets, solvent; chloroform: methanol = 10:1) to give 3-(2-pyrimidinylmethylaminocarbonyl)-6-(2-hydroxymethyl-1-pyrrolidiny)-4-(3-chloro-4-methoxybenzylamino)pyridine 43mg as a pale brown powder. MS(m/z): 483(M+H)<sup>+</sup>

#### Examples 305-306

Each compound listed in the following Table 11 is prepared by treating a corresponding starting compound in the same manner as Example 304.

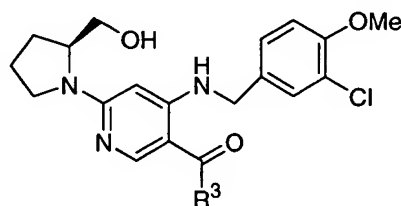
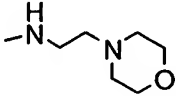
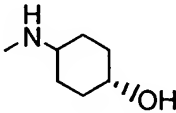




Table 11

Example No.	R <sup>3</sup>	Physical property etc.
305		Amorphous MS(m/z):504(M+H) <sup>+</sup>
306		mp: 179.5-182.5°C

## Example 307

(1) To a solution of diisopropylamine 3.76g in tetrahydrofuran 25ml is dropped at -78°C n-butyllithium (23.2ml). The mixture is stirred at 0°C for 10 minutes and thereto is added 2,6-dichloropyridine 5.0g in tetrahydrofuran 25ml at -78°C over a period of 20 minutes. The mixture is stirred at -78°C for 3 hours. The reaction mixture is poured into powdered dry ice and is left at room temperature overnight. After removal of the solvent the residue is dissolved in a mixture of ethyl acetate and a 10% aqueous sodium hydroxide solution, and the water layer is separated and made acid with concentrated hydrochloric acid. The resulting colorless precipitate is filtered and washed with cold water to give 2,6-dichloronicotinic acid 4.50g. mp 148-150°C, MS(ESI): 190(M-H)<sup>-</sup>

(2) A mixture of the compound (prepared in the above (1)) 500mg, 3-chloro-4-methoxybenzylamine 638mg, potassium carbonate 817mg, copper bromide 313mg and 1-methyl-2-pyrrolidinone 10ml is stirred at 120°C for 2.5 hours. After cooling to room temperature thereto are added ethyl acetate and 1N hydrochloric acid. The organic layer is separated, washed with water (twice) and brine, and dried over sodium sulfate. After removal of sodium sulfate, the filtrate is concentrated in vacuo, and the residue is purified with column chromatography (silica gel 30g, solvent; chloroform→chloroform:methanol = 70:1) to give 2-(3-chloro-4-methoxybenzylamino)-6-chloronicotinic acid as colorless crystals, 471mg. mp 184-185.5°C, MS(m/z): 325(M-H)<sup>-</sup>

(3) A mixture of the compound (prepared in the above (2)) 200mg and ethanol 10ml is saturated with hydrogen chloride gas at 0°C and is refluxed for 14 hours. The mixture is again saturated with hydrogen chloride and is refluxed for 4 hours. After removal of the solvent the residue is diluted with a mixture of ethyl acetate and an aqueous sodium hydrogen carbonate solution, and the organic layer is purified with column chromatography (silica gel 25g, solvent; hexane→hexane:ethyl acetate = 20:1, then silica gel 25g, solvent; chloroform: hexane = 1:1) to give 2-(3-chloro-4-methoxybenzylamino)-6-chloronicotinic acid ethyl ester as colorless crystals, 84mg. mp 108-112.5°C, MS(m/z): 355(M+H)<sup>+</sup>

(4) A mixture of the compound (prepared in the above (2)) 150mg, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide · hydrochloride 132mg, 1-hydroxybenzotriazole 93mg, 2-aminomethylpyrimidine 75mg and dimethylformamide 3ml is stirred for 16 hours at room temperature. To the mixture are added ethyl acetate and an aqueous sodium hydrogen carbonate solution, and the organic layer is washed with water (three times) and brine and dried over sodium sulfate. After removal of the sodium sulfate, the filtrate is concentrated in vacuo, and the residue is purified with column chromatography (silica gel 25g, solvent; chloroform: methanol= 50:1) to give 2-(3-chloro-4-methoxybenzylamino) -6-chloro-3-(2-pyrimidinylmethyl aminocarbonyl)pyridine as a pale yellow amorphous, 179mg. MS(m/z): 418(M+H)<sup>+</sup>

(5) A mixture of the compound (prepared in the above (4)) 159mg, prolinol 192mg and 1-methyl-2-pyrrolidinone 3ml is stirred at 200°C for 2 hours. After the mixture is cooled to room temperature, ethyl acetate and water are added to the mixture and the organic layer is separated, washed with water (five times) and brine, and dried over sodium sulfate. After removal of the sodium sulfate by filtration, the filtrate is concentrated in vacuo, and the residue is purified with preparative thin-layer

chromatography (2 sheets, solvent; chloroform: methanol=10:1, and then 2 sheets, solvent; ethyl acetate) to give 2-(3-chloro-4-methoxybenzylamino)-6-(2-hydroxymethyl-1-pyrrolidinyl)-3-(2-pyrimidinylmethylaminocarbonyl)pyridine as a colorless amorphous 119mg. MS(m/z): 483(M+H)<sup>+</sup>

#### Examples 308-309

Each compound listed in the following Table 12 is prepared by treating a corresponding starting compound in the same manner as Example 307.

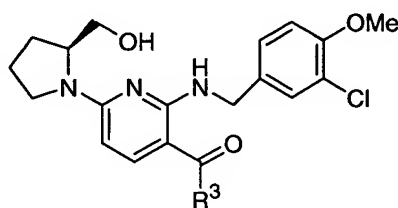


Table 12

Example No.	R <sup>3</sup>	Physical property etc.
308		Amorphous MS(m/z):504(M+H) <sup>+</sup>
309		Amorphous MS(m/z):489(M+H) <sup>+</sup>

#### Example 310

(1) To a mixture of 3-ketoglutaric acid dimethyl ester 15.0g, triethylamine 9.6g and acetonitrile 300ml is portionwise added 4-acetylamino benzensulfonylazide 20.7g at 0°C. The mixture is stirred at room temperature for 30 minutes. After removal of the precipitate by filtration the filtrate is concentrated in vacuo. The residue is diluted with a mixture of hexane and diethyl ether (1:1). The insoluble materials are removed by filtration and the filtrate is concentrated in vacuo. The residue is purified with column

chromatography (silica gel 225g, solvent; hexane: ethyl acetate= 5:1→3:1) to give 2-diazo-3-ketoglutaric acid dimethyl ester as a pale yellow oil, 16.03g.

(2) A mixture of the compound (prepared in the above (1)) 17.08g, triphenylphosphine 22.4g and diethyl ether 170ml is stirred at room temperature for 15 hours. The solvent is removed in vacuo and the resulting pale yellow solid-like residue is diluted with a mixture of acetic acid 170ml and water 17ml, and the mixture is refluxed for 9.5 hours. The solvent is removed in vacuo and the residue is mixed with silica gel 50g in a mixture of chloroform and methanol (1:1) and purified with column chromatography (silica gel 400g, solvent; chloroform: methanol = 50:1→5:1) and triturated with diethyl ether to give 4,6-dihydroxypyridazine carboxylic acid methyl ester as pale yellow crystals, 8.065g. mp 216-218°C(decomposition)

(3) A mixture of the compound (prepared in the above (2)) 8.06g and phosphoryl chloride 80ml is stirred at 100°C for 4 hours. After removal of the excess phosphoryl chloride, the residue is poured into ice-water and extracted with ethyl acetate, washed with water (twice) and brine, and dried over sodium sulfate. After removal of the sodium sulfate, the filtrate is concentrated in vacuo, and the residue is purified with column chromatography (silica gel 200g, solvent; hexane: ethyl acetate = 4:1) to give 3-methoxycarbonyl-4,6-dichloropyridazine as colorless crystals 7.44g. mp 57-59.5°C

(4) A mixture of the compound (prepared in the above (3)) 150g and 3-chloro-4-methoxybenzylamine 1.37g, triethylamine 1.1g and toluene 30ml is stirred at room temperature for 6 hours. Further 3-chloro-4-methoxybenzylamine 250mg is added thereto and the mixture is stirred at room temperature for additional 17 hours. Ethyl acetate and an aqueous sodium hydrogen carbonate solution are added thereto and the organic layer is washed with water and brine, and dried over sodium sulfate. After removal of the sodium sulfate, the filtrate is concentrated in vacuo, and the residue is

trituated with diethyl ether to give a colorless solid 2.34g. mp159-161°C. The solid is purified with silica gel chromatography (silica gel 100g, solvent; chloroform) to give 3-methoxycarbonyl-6-chloro-4-(3-chloro-4-methoxybenzylamino)pyridazine 1.89g. mp 162-163°C, MS(m/z): 342(M+H)<sup>+</sup>

(5) A mixture of the compound (prepared in the above (4)) 800mg, prolinol 273mg, triethylamine 496mg and 1-methyl-2-pyrrolidinone 10ml is stirred at 50°C for 4 hours, and then at 80°C for 8 hours. After the mixture is cooled to room temperature, ethyl acetate and an aqueous sodium hydrogen carbonate solution are added to the mixture, and the organic layer is washed with water and brine, and dried over sodium sulfate. After removal of the sodium sulfate, the filtrate is concentrated in vacuo, and the residue is purified with column chromatography (silica gel 50g, solvent; ethyl acetate→ethyl acetate: ethanol = 5:1) to give 3-methoxycarbonyl-6-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)pyridazine as a colorless powder. MS(m/z): 407(M+H)<sup>+</sup>

(6) A mixture of the compound (prepared in the above (4)) 500mg, a 10% aqueous sodium hydroxide solution 5ml and dimethyl sulfoxide 10ml is stirred at room temperature for 4 hours. The mixture is acidified (pH about 5) at 0°C with conc. hydrochloric acid. Water is added thereto and the precipitate is collected, washed with water and dried in vacuo to give 6-chloro-4-(3-chloro-4-methoxybenzylamino)pyridazine-3-carboxylic acid 487mg. mp 155-157°C(decomposition) MS(m/z): 326(M-H)<sup>-</sup>

(7) A mixture of the compound (prepared in the above (6)) 100mg, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide · hydrochloride 88mg, 1-hydroxybenzotriazole 62mg, 2-aminomethylpyrimidine 50mg and dimethylformamide 3ml is stirred for 4 days at room temperature. To the mixture are added ethyl acetate and an aqueous sodium hydrogen

carbonate solution, and the organic layer is washed with water (four times) and brine and dried over sodium sulfate. After removal of sodium sulfate, the filtrate is concentrated in vacuo, and the residue is triturated with diethyl ether to give 3-(2-pyrimidinylmethylaminocarbonyl)-6-chloro-4-(3-chloro-4-methoxybenzylamino)pyridazine as a colorless solid, 105mg. mp 165-180°C(decomposition), MS(m/z): 418(M+H)<sup>+</sup>

(8) A mixture of the compound (prepared in the above (7)) 94mg, prolinol 113mg and 1-methyl-2-pyrrolidinone 3ml is stirred at 120°C for 6 hours. After the mixture is cooled to room temperature, ethyl acetate and water are added to the mixture, and the organic layer is washed with water (five times) and brine, and dried over sodium sulfate. After removal of the sodium sulfate, the filtrate is concentrated in vacuo, and the residue is purified with preparative thin-layer chromatography (3 sheets, solvent; chloroform: methanol = 10:1) and triturated with diethyl ether to give 3-(2-pyrimidinylmethylaminocarbonyl)-6-(2-hydroxymethyl-1-pyrrolidinyl-4-(3-chloro-4-methoxybenzylamino)pyridazine as colorless crystals, 51mg. mp 168-170.5°C, MS(m/z): 484(M+H)<sup>+</sup>

#### Examples 311-312

Each compound listed in the following Table 13 is prepared by treating a corresponding starting compound in the same manner as Example 310.

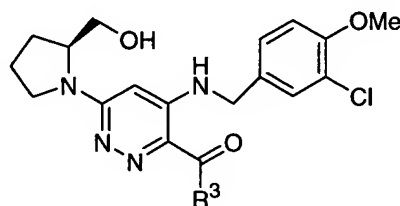
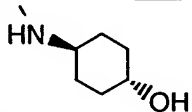
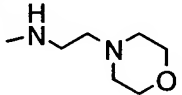


Table 13

Example No.	R <sup>3</sup>	Physical property etc.
311		mp: 205-207°C MS(m/z):490(M+H) <sup>+</sup>
312		Amorphous MS(m/z):505(M+H) <sup>+</sup>

## Example 313

(1) A mixture of 3-methylthio-5-hydroxy-6-ethoxycarbonyl-1,2,4-triazine (see Chem. Ber., 2179-2184, 97 (1964)) 546mg and thionyl chloride 10ml is stirred at 60-70°C for 5 hours. The mixture is concentrated in vacuo, and to the residue is added 3-chloro-4-methoxybenzylamine hydrochloride 634mg and dimethylformamide 20ml, and further triethylamine 770mg in dimethylformamide 20ml. After stirring for 3 hours at room temperature, the mixture is poured into water and extracted with ethyl acetate. The combined ethyl acetate layer is washed with water and brine, concentrated in vacuo. The residue is purified with silica gel chromatography (solvent; chloroform: methanol = 50:1) to give 3-methylthio-5-(3-chloro-4-methoxybenzylamino)-6-ethoxycarbonyl-1,2,4-triazine as a pale yellow solid, 769mg. mp 101-105°C MS(m/z): 369(M+H)<sup>+</sup>

(2) A solution of m-chloroperbenzoic acid (70-75%) 900mg in chloroform 10ml is dropped at 5°C to the compound (prepared in the above (1)) 1.261g in chloroform 20ml. Three hours later thereto are added a solution of L-prolinol 380mg and triethylamine 400mg in chloroform 10ml. The mixture is stirred for 5 hours at room temperature. The chloroform layer is washed with water, an aqueous sodium hydrogen carbonate solution, water and brine in order, and dried in vacuo. The residue is purified with neutral silica gel chromatography (solvent; chloroform: methanol = 20:1) to give 3-(2-hydroxymethyl-

1-pyrrolidinyl)-5-(3-chloro-4-methoxybenzylamino)-6-ethoxycarbonyl-1,2,4-triazine as a white powder 719mg. MS(m/z): 422(M+H)<sup>+</sup>

(3) A solution of sodium hydroxide 250mg in water 4ml is added to the compound (prepare in the above (2)) 700mg in dimethyl sulfoxide 20ml at 10°C. Then the mixture is stirred for 3 hours at room temperature. The mixture is neutralized (pH 6-7) with water 50ml and a 10% aqueous citric acid solution and extracted with ethyl acetate. The ethyl acetate layer is washed with an aqueous sodium chloride solution, dried and distilled to give crude 3-(2-hydroxymethyl-1-pyrrolidinyl)-5-(3-chloro-4-methoxybenzylamino)-6-carboxy-1,2,4-triazine as a pale brown amorphous, 416mg. MS(m/z): 392(M+H)<sup>+</sup>

(4) To a mixture of the compound (prepared in the above (3)) 150mg, 1-hydroxybenzotriazole 57mg and 2-aminomethylpyrimidine 65mg in dimethylformamide is added at 100°C 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide · hydrochloride 81mg. The mixture is stirred at room temperature for 20 hours and poured into water containing sodium hydrogen carbonate and extracted with ethyl acetate. The combined ethyl acetate layer is washed with water (four times) and brine, dried over sodium sulfate and concentrated in vacuo. The residue is purified with silica gel chromatography (solvent; chloroform: methanol = 50:1 → 20:1) and the main fraction is crystallized from a mixture of ethyl acetate and hexane to give 3-(2-hydroxymethyl-1-pyrrolidinyl)-5-(3-chloro-4-methoxybenzylamino)-6-(2-pyrimidinylmethylaminocarbonyl)-1,2,4-triazine 85mg. mp 170-173°C MS(m/z): 485(M+H)<sup>+</sup>

#### Examples 314-315

Each compound listed in the following Table 14 is prepared by treating a corresponding starting compound in the same manner as Example 313.



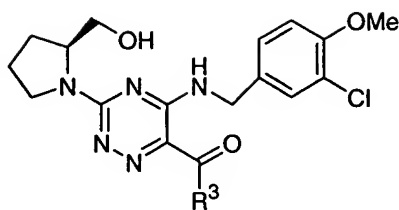


Table 14

Example No.	R <sup>3</sup>	Physical property etc.
314		Powder MS(m/z):491(M+H) <sup>+</sup>
315		Powder MS(m/z):506(M+H) <sup>+</sup>

#### Example 316

(1) 3,5-Dibromopyridine 2.37g is dissolved in methylene chloride 25ml and thereto is added m-chloroperbenzoic acid 2.96g at room temperature under stirring. After stirring for 5 hours at room temperature, additional m-chloroperbenzoic acid 246mg is added thereto and the mixture is stirred. After 15 hours the solvent is removed in vacuo and the residue is purified by silica gel chromatography (solvent; n-hexane: ethyl acetate = 1:1) to give 3,5-dibromopyridine N-oxide as colorless crystals, 2.26g. mp 140-142°C

(2) A mixture of 3,5-dibromopyridine N-oxide (prepared in the above (1)) 2.26g, trimethylsilylcyanide 1.06g and dimethylcarbamic acid chloride 1.15g in methylene chloride 25ml is refluxed under heating for 1 day. To the mixture are added trimethylsilylcyanide 443mg and dimethylcarbamic acid chloride 480mg, and the mixture is refluxed under heating for 20 hours. An aqueous sodium hydrogen carbonate solution is added to the reaction mixture cooled, and the mixture is extracted with methylene chloride. The combined extract is washed, dried and the solvent is removed

in vacuo. The residue is purified by silica gel chromatography (solvent; n-hexane: ethyl acetate = 1:1) to give 2-cyano-3,5-dibromopyridine 1.38g. mp 109-112°C

(3) 2-Cyano-3,5-dibromopyridine (prepared in the above (2)) 3.27g is added to a mixture of acetic acid 14ml, sulfuric acid 14ml and water 14ml, and the mixture is refluxed at 140°C for 4 hours. The reaction mixture is cooled and water is added thereto. The resulting precipitate is filtered and washed with water. The precipitate is dissolved in ether, washed and dried. The solvent is removed in vacuo and crystallized from a mixture of ether and hexane to give 3,5-dibromopyridine-2-carboxylic acid. mp 170-171°C

(4) In N-methylpyrrolidone 6ml are suspended 3,5-dibromopyridine-2-carboxylic acid (prepared in the above (3)) 561mg, 3-chloro-4-methoxybenzylamine 1.71g, copper bromide 315mg and potassium carbonate 912mg, and the suspension is stirred at 120°C for 17 hours. To the reaction mixture are added 1N hydrochloric acid and ethyl acetate, and the precipitate is filtered and washed with water and aqueous ammonia. On the other hand the filtrate, ethyl acetate layer is also washed with water and aqueous ammonia. The precipitate previously obtained and the ethyl acetate layer are combined and the solvent is removed in vacuo. The residue is purified by NH-silica gel chromatography (solvent; chloroform: methanol = 50:1-20:1) to give 5-bromo-3-(3-chloro-4-methoxybenzylamino)pyridine-2-carboxylic acid as a pale yellow powder, 300mg.

(5) In N,N-dimethylformamide 3ml are suspended 5-bromo-3-(3-chloro-4-methoxybenzylamino)pyridine-2-carboxylic acid (prepared in the above (4)) 102mg, diethylcyanophosphonate 67mg, triethylamine 83mg and 2-aminomethylpyrimidine 90mg, and the suspension is stirred at room temperature for 7 hours. To the reaction mixture is added diethylcyanophosphonate 67mg, and the mixture is stirred at room temperature for 4 hours. Further diethylcyanophosphonate 67mg and 2-

aminomethylpyrimidine 90mg are added thereto and the mixture is stirred at room temperature for 15 hours. An aqueous sodium hydrogen carbonate solution is added to the reaction mixture, and the mixture is extracted with ethyl acetate. The organic layer is washed and dried, and then the solvent is removed in vacuo. The residue is purified by silica gel chromatography (solvent; chloroform) and crystallized from ether to give 5-bromo-3-(3-chloro-4-methoxybenzylamino)-2-(2-pyrimidinylmethylaminocarbonyl)pyridine as pale yellow crystals 55mg. mp 179-183°C(decomposition)

(6) In diglyme 2ml are suspended 5-bromo-3-(3-chloro-4-methoxybenzylamino)-2-(2-pyrimidinylmethylaminocarbonyl)pyridine (prepared in the above (5)) 20mg, trisdibenzylidene acetone palladium (0) 22mg, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl 4mg, cesium carbonate 43mg and L-prolinol 88mg, and the mixture is stirred at 120°C for 5 hours. An aqueous saturated sodium hydrogen carbonate solution is added to the reaction mixture cooled, and the mixture is extracted with ethyl acetate. The combined organic layer is washed, dried and the solvent is removed in vacuo. The residue is purified by silica gel preparative thin-layer chromatography (developing solution; ethyl acetate) to give (S)-(3-chloro-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl)-2-(2-pyrimidinylmethylaminocarbonyl)pyridine as a pale brown powder 5.2mg. MS(m/z): 483(M+H)<sup>+</sup>

#### Example 317

The following compound is obtained from 5-bromo-3-(3-chloro-4-methoxybenzylamino)pyridine-2-carboxylic acid in the same manner as Example 316 (5) and (6).

: 3-(3-Chloro-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl)-2-(2-morpholinylethylaminocarbonyl)pyridine. MS(m/z): 505(M+H)<sup>+</sup>

#### Example 318

(1) A mixture of diisopropylamine 2.54g, a 1.6M solution of n-butyl lithium in hexane 15.7ml and tetrahydrofuran 100ml is stirred for 30 minutes on a dry ice-acetone bath. Thereto is added 2,4,6-trichloropyrimidine 2.00g in tetrahydrofuran 8ml over a period of 30 minutes, followed by further one hour agitation. The reaction mixture is poured into dry ice, and the mixture is stirred for a hour at room temperature. The reaction mixture is made acidic with 10% hydrochloric acid 20ml, diluted with an aqueous saturated sodium chloride solution and extracted with ethyl acetate. The organic layer is washed, dried and concentrated in vacuo. The solvent is removed by azeotrope with chloroform and the resulting hemisolid is triturated with hexane to give 5-carboxy-2,4,6-trichloropyrimidine as a crystalline powder, 1.51g. mp 150-153°C

(2) To a mixture of 5-carboxy-2,4,6-trichloropyrimidine (prepared in the above (1)) 100mg, triethylamine 89mg in dimethylformamide 3ml is added at room temperature a 1.0M solution of benzylthiol in tetrahydrofuran 0.44ml, and the mixture is stirred for 1 hour. The reaction mixture is diluted with a 10% aqueous citric acid solution and extracted with ethyl acetate. The organic layer is washed, dried and concentrated in vacuo to give 4-benzylthio-5-carboxy-2,6-dichloropyrimidine as a pale yellow oil.

(3) A mixture of whole amount of 4-benzylthio-5-carboxy-2,6-dichloropyrimidine prepared in the above (2), sodium hydrogen carbonate 55mg, methyl iodide 0.2ml, dimethylformamide 3ml and tetrahydrofuran 1ml is stirred at room temperature for 1 hour. The reaction mixture is diluted with a 10% aqueous citric acid solution and extracted with ethyl acetate. The organic layer is washed, dried and concentrated in

vacuo. The residue is separated with preparative thin-layer chromatography (solvent; hexane: ethyl acetate = 10:1) to give a mixture of 4-benzylthio-5-methoxycarbonyl-2,6-dichloropyrimidine and 4,6-dibenzylthio-5-methoxycarbonyl-2-chloropyrimidine as a colorless oil, 123mg.

(4) A mixture of 4-benzylthio-5-methoxycarbonyl-2,6-dichloropyrimidine and 4,6-dibenzylthio-5-methoxycarbonyl-2-chloropyrimidine (prepared in the above (3)) 97mg, 4-hydroxypiperidine 29mg, triethylamine 29mg and toluene 2.5mg is stirred at room temperature for 4 hours. Further, 4-hydroxypiperidine 3mg and triethylamine 3mg are added thereto, and the mixture is stirred for 30 minutes. The reaction mixture is diluted with a 10% aqueous citric acid solution and extracted with ethyl acetate. The organic layer is washed, dried and concentrated in vacuo to give 4-benzylthio-5-methoxycarbonyl-6-(4-hydroxypiperidine-1-yl)-2-chloropyrimidine as a colorless caramel, 120mg.

(5) A mixture of 4-benzylthio-5-methoxycarbonyl-6-(4-hydroxypiperidine-1-yl)-2-chloropyrimidine (prepared in the above (4)) 120mg, 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine 70mg, triethylamine 57mg and N,N-dimethylacetamide 3ml is stirred at 10°C for 3 hours. The reaction mixture is diluted with an aqueous citric acid solution and extracted with ethyl acetate. The water layer is made basic with an aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer is washed, dried and concentrated in vacuo to give 4-benzylthio-5-methoxycarbonyl-6-(4-hydroxypiperidin-1-yl)-2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)pyrimidine as a colorless foam, 105mg.

IR (Neat+CHCl<sub>3</sub>)cm<sup>-1</sup>: 3050-3600, 1695, 1533, 1503, 1433

APCI-MS(m/z): 481(M+H)<sup>+</sup>

(6) To a solution of 4-benzylthio-5-methoxycarbonyl-6-(4-hydroxypiperidin-1-yl)-2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)pyrimidine (prepared in the above (5)) 93mg in chloroform 2.5ml is dropped a solution of m-chloroperbenzoic acid 44mg in chloroform 4ml over a period of 10 minutes on a ice bath, and the mixture is stirred for 1.5 hours. The mixture is diluted with an aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer is washed, dried and concentrated in vacuo to give 4-benzylsulfinyl-5-methoxycarbonyl-6-(4-hydroxypiperidin-1-yl)-2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)pyrimidine as a slightly yellow foam, 83mg.

(7) A mixture of 4-benzylsulfinyl-5-methoxycarbonyl-6-(4-hydroxypiperidin-1-yl)-2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)pyrimidine (prepared in the above (6)) 83mg, 3-chloro-4-methoxybenzylamine 86mg, triethylamine 51mg and N,N-dimethylacetamide 3ml is stirred at 110°C for 1 hour. The reaction mixture is diluted with ice water and extracted with ethyl acetate. The organic layer is washed, dried and concentrated in vacuo. The residue is separated with silica gel chromatography (solvent; ethyl acetate→ ethyl acetate: methanol = 15:1→10:1) and crystallized from a mixture of methanol, ethyl acetate and isopropyl ether to give 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-(4-hydroxypiperidin-1-yl)-2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)pyrimidine as a colorless crystalline powder 43mg.  
mp 192-194°C

IR (Nujol)cm<sup>-1</sup>: 3380, 1664, 1572, 1533, 1433

APCI-MS(m/z): 528(M+H)<sup>+</sup>

### Example 319

(1) A N,N-dimethylformamide solution 6ml of 3-chloro-4-methoxybenzylamine 1.51g and triethylamine 2.46g is dropped over a period of 25 minutes under ice cooling

a solution of 5-carboxy-2,4,6-trichloropyrimidine (prepared in Example 318(1)) 2.00g in N,N-dimethylformamide 12ml, and the mixture is further stirred for 90 minutes. The reaction mixture is diluted with a 10% aqueous citric acid solution and extracted with ethyl acetate. The combined extract is washed with water and an aqueous sodium chloride solution, dried over anhydrous sodium sulfate and concentrated in vacuo to give 4-(3-chloro-4-methoxybenzylamino)-2,6-dichloropyrimidine-5-carboxylic acid as a pale brown crystalline powder 2.92g. mp 144-151°C

(2) To a mixture of 11ml of the carboxylic acid (prepared in the above (1)) 2.92g and sodium hydrogen carbonate 0.744g in N,N-dimethylformamide is added methyl iodide 1.00ml, and the mixture is stirred at room temperature for 16 hours. The reaction mixture is diluted with a 10% aqueous citric acid solution and extracted with ethyl acetate. The combined extract is washed with water and an aqueous saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue is separated with silica gel chromatography (After effluence with solvent (hexane: chloroform = 2:1), solvent; hexane:chloroform:ethyl acetate = 20:10:1) to give 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-2,6-dichloropyrimidine as a colorless crystalline powder 2.31g. mp 119-121°C

IR (Nujol)cm<sup>-1</sup>: 3320, 1689, 1591, 1573, 1507, 1460

APCI-MS(m/z): 376(M+H)<sup>+</sup>

(3) A mixture of 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-2,6-dichloropyrimidine (prepared in the above (2)) 150mg, a 1.0M solution of benzylthiol in dimethylformamide 0.40ml, triethylamine 40mg and dimethylformamide 2.5ml is stirred at room temperature for 2.5 days. The reaction mixture is diluted with water and extracted with ethyl acetate. The organic layer is washed, dried and concentrated in vacuo. The residue is separated with preparative thin-layer chromatography (solvent;

hexane: chloroform: ethyl acetate = 30:30:4) and crystallized from isopropyl ether to give 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-chloro-2-benzylthiopyrimidine as a colorless crystalline powder 125mg. mp 89-90°C

(4) A mixture of 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-chloro-2-benzylthiopyrimidine (prepared in the above (3)) 108mg, 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine 57mg, triethylamine 47mg and N,N-dimethylacetamide 2.5ml is stirred at 60°C for 1 hour. The reaction mixture is diluted with water and extracted with ethyl acetate. The organic layer is washed, dried and concentrated in vacuo. The residue is separated with silica gel chromatography (solvent; chloroform: methanol = 200:1) to give 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-2-benzylthiopyrimidine as a colorless foam, 129mg.

IR (Nujol)cm<sup>-1</sup>: 3335, 1665, 1567, 1518, 1503, 1456

APCI-MS(m/z): 551(M+H)<sup>+</sup>

(5) To a chloroform solution 2ml of 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-2-benzylthiopyrimidine (prepared in the above (4)) 104mg is dropped a solution of m-chloroperbenzoic acid 43mg in chloroform 3ml over a period of 20 minutes on an ice bath, and the mixture is stirred for 1 hour. The reaction mixture is diluted with an aqueous saturated sodium hydrogen carbonate and extracted with ethyl acetate. The organic layer is washed, dried and concentrated in vacuo to give 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-2-benzylsulfinylpyrimidine as a slightly yellow caramel.

(6) A mixture of whole amount of 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-2-



benzylsulfinylpyrimidine (prepared in the above (5)), 4-hydroxypiperidine 57mg, triethylamine 57mg and N,N-dimethylacetamide 3ml is stirred at 60°C for 1.5 hours. After cooling the reaction mixture is diluted with ice water and extracted with ethyl acetate. The organic layer is washed, dried and concentrated in vacuo. The residue is crystallized from a mixture of ethyl acetate and isopropyl ether to give of 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-2-(4-hydroxypiperidin-1-yl)pyrimidine as a colorless crystalline powder 75mg.

mp 191-194°C

IR (Nujol)cm<sup>-1</sup>: 3342, 3167, 1648, 1567, 1529, 1462, 1441

APCI-MS(m/z): 528(M+H)<sup>+</sup>

#### Example 320

(1) To a solution of diisopropylamine 11.93g in tetrahydrofuran 350ml is dropped a 1.6M solution of n-butyl lithium in hexane 73.7ml over a period of 20 minutes on dry ice-acetone bath, and the mixture is stirred for 30 minutes. Thereto is added 4,6-dichloro-2-methylthiopyrimidine 10.00g in tetrahydrofuran 50ml over a period of 1 hour on a dry ice-acetone bath, followed by further one hour agitation. The reaction mixture is poured into dry ice and the mixture is stirred for 1.5 hours at room temperature. The reaction mixture is made acidic with 10% hydrochloric acid, diluted with water and extracted with ethyl acetate. The organic layer is washed, dried and condensed in vacuo. The resulting solid is triturated with hexane to give 4,6-dichloro-5-carboxy-2-methylthiopyrimidine as a brown crystalline powder, 10.42g. mp 151-

158°C(decomposition)

IR (Nujol)cm<sup>-1</sup>: 1707, 1547, 1377

ESI-MS(m/z): 237(M-H)<sup>-</sup>

(2) To a mixture of 4,6-dichloro-5-carboxy-2-methylthiopyrimidine (prepared in the above (1)) 500mg and triethylamine 0.58ml in dimethylformamide 3ml is added 3-chloro-4-methoxybenzylamine 359mg in dimethylformamide 3ml at room temperature over a period of 15 minutes, and the mixture is stirred for 4 hour. The reaction mixture is diluted with a 10% aqueous citric acid solution and extracted with ethyl acetate. The organic layer is washed, dried and concentrated in vacuo to give 4-(3-chloro-4-methoxybenzylamino)-5-carboxy-6-chloro-2-methylthiopyrimidine as a slightly brown powder.

(3) A mixture of whole amount of 4-(3-chloro-4-methoxybenzylamino)-5-carboxy-6-chloro-2-methylthiopyrimidine prepared in the above (2), sodium hydrogen carbonate 193mg, methyl iodide 0.20ml and dimethylformamide 4ml is stirred at room temperature for 3 hours. Further, methyl iodide 0.13ml is added thereto and the mixture is stirred for 12 hours. The reaction mixture is diluted a 10% aqueous citric acid solution and extracted with ethyl acetate. The organic layer is washed, dried and concentrated in vacuo. The residue is separated with silica gel chromatography (solvent; hexane: chloroform: ethyl acetate = 20:10:1) to give 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-chloro-2-methylthiopyrimidine as a colorless crystalline powder 441mg. mp 105-108°C

(4) A mixture of 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-chloro-2-methylthiopyrimidine (prepared in the above (3)) 100mg, 4-hydroxypiperidine 78mg, triethylamine 0.11ml and N,N-dimethylacetamide 3ml is stirred at room temperature for 1 hour. The reaction mixture is diluted a 10% aqueous citric acid solution and extracted with ethyl acetate. The organic layer is washed, dried and concentrated in vacuo to give 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-(4-hydroxypiperidin-1-yl)-2-methylthiopyrimidine as a colorless caramel 132mg.

IR (Neat+CHCl<sub>3</sub>)cm<sup>-1</sup>: 3345, 1663, 1569, 1519

APCI-MS(m/z): 453(M+H)<sup>+</sup>

(5) A mixture of 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-(4-hydroxypiperidin-1-yl)-2-methylthiopyrimidine (prepared in the above (4)) 121mg in chloroform 3ml is dropped a solution of m-chloroperbenzoic acid 54mg in chloroform 4ml on an ice bath over a period of 15 minutes, and the mixture is stirred for 1 hour. The reaction mixture is diluted with an aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer is washed, dried and concentrated in vacuo to give 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-(4-hydroxypiperidin-1yl)-2-methylsulfinylpyrimidine as a colorless caramel.

(6) A mixture of whole amount of 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-(4-hydroxypiperidin-1-yl)-2-methylsulfinylpyrimidine (prepared in the above (5)), 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine 73mg, triethylamine 0.083ml and N,N-dimethylacetamide 4ml is stirred at 110°C for 4 hours. After cooling the reaction mixture is diluted with a 10% aqueous citric acid solution and washed with ethyl acetate. The organic layer is extracted with a 10% aqueous citric acid solution. The water layer is made basic with sodium hydrogen carbonate and extracted with ethyl acetate. The ethyl acetate layer is washed, dried and concentrated in vacuo. The residue is separated with silica gel chromatography (solvent; chloroform: methanol = 100:1→50:1), and then crystallized from a mixture of ethyl acetate, methanol and isopropyl ether to give 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-(4-hydroxypiperidin-1-yl)-2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)pyrimidine as a colorless crystalline powder 20mg.

mp 179-180°C

IR (Nujol)cm<sup>-1</sup>: 3380, 3181, 1664, 1572, 1533, 1463

APCI-MS(m/z): 528(M+H)<sup>+</sup>

#### Example 321

(1) A mixture of 4-(3-chloro-4-methoxybenzylamino)-5-carboxy-6-chloro-2-methylthiopyrimidine 500mg and thionyl chloride 2ml is refluxed for 10 minutes. After reaction thionyl chloride is removed and the solvent is removed in azeotrope with methylene chloride to give 4-(3-chloro-4-methoxybenzylamino)-5-chloroformyl-6-chloro-2-methylthiopyrimidine.

(2) A mixture of whole amount of 4-(3-chloro-4-methoxybenzylamino)-5-chloroformyl-6-chloro-2-methylthiopyrimidine (prepared in the above (1)), methylene chloride 15ml and 2-benzyloxyethanol 224mg is refluxed for 30 minutes. After cooling the reaction mixture is diluted with water and neutralized with an aqueous saturated sodium hydrogen carbonate solution. The solution is washed with ethyl acetate. The methylene chloride layer is diluted with ethyl acetate, washed, dried and concentrated in vacuo. The residue is separated with silica gel chromatography (solvent; hexane: ethyl acetate = 5:1) to give 4-(3-chloro-4-methoxybenzylamino)-5-(2-benzyloxyethoxycarbonyl)-6-chloro-2-methylthiopyrimidine as a colorless oil 655mg. IR (Neat)cm<sup>-1</sup>: 3340, 1731, 1674, 1567, 1555, 1503

APCI-MS(m/z): 508(M+H)<sup>+</sup>

(3) A mixture of 4-(3-chloro-4-methoxybenzylamino)-5-(2-benzyloxyethoxycarbonyl)-6-chloro-2-methylthiopyrimidine (prepared in the above (2)) 636mg, 4-hydroxypiperidine 190mg, triethylamine 0.26ml and dimethylformamide 4ml is stirred at room temperature for 30 minutes. The reaction mixture is diluted a 10% aqueous citric acid solution and extracted with ethyl acetate. The organic layer is washed, dried and concentrated in vacuo to give 4-(3-chloro-4-methoxybenzylamino)-5-

(2-benzyloxyethoxycarbonyl-6-(4-hydroxypiperidin-1-yl)-2-methylthiopyrimidine as a colorless caramel, 713mg.

IR (Neat+CHCl<sub>3</sub>)cm<sup>-1</sup>: 3351, 1661, 1568, 1519

APCI-MS(m/z): 573(M+H)<sup>+</sup>

(4) To a solution of 4-(3-chloro-4-methoxybenzylamino)-5-(2-benzyloxyethoxycarbonyl)-6-(4-hydroxypiperidin-1-yl)-2-methylthiopyrimidine (prepared in the above (3)) 100mg in methylene chloride 3ml is added at room temperature a solution of m-chloroperbenzoic acid 79mg in methylene chloride 2ml, and the mixture is stirred for 30 minutes. The reaction mixture is diluted with an aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer is washed, dried and concentrated in vacuo to give 4-(3-chloro-4-methoxybenzylamino)-5-(2-benzyloxyethoxycarbonyl)-6-(4-hydroxypiperidin-1-yl)-2-methylsulfinylpyrimidine.

(5) A mixture of whole amount of 4-(3-chloro-4-methoxybenzylamino)-5-(2-benzyloxyethoxycarbonyl)-6-(4-hydroxypiperidin-1-yl)-2-methylsulfinylpyrimidine (prepared in the above (4)), L-prolinol 53mg, triethylamine 53mg and dimethylformamide 4ml is stirred at room temperature for 1.5 hours and then at 65°C for 3.5 hours. After cooling the reaction mixture is diluted with water and extracted with ethyl acetate. The ethyl acetate layer is washed, dried and concentrated in vacuo. The residue is separated with silica gel chromatography (solvent; chloroform: ethyl acetate = 1:2) to give 4-(3-chloro-4-methoxybenzylamino)-5-(2-benzyloxyethoxycarbonyl)-6-(4-hydroxypiperidin-1-yl)-2-(2-hydroxymethyl-1-pyrrolidinyl)pyrimidine as a colorless caramel 96mg.

IR (Neat+CHCl<sub>3</sub>)cm<sup>-1</sup>: 3345, 1650, 1573, 1528, 1501, 1454

APCI-MS(m/z): 626(M+H)<sup>+</sup>

(6) A mixture of 4-(3-chloro-4-methoxybenzylamino)-5-(2-benzyloxyethoxycarbonyl)-6-(4-hydroxypiperidin-1-yl)-2-(2-hydroxymethyl-1-pyrrolidinyl)pyrimidine (prepared in the above (5)) 60mg, 28% sodium methoxide/methanol 185mg and tetrahydrofuran 2.5ml is stirred at 60°C for 2.5 hours. After cooling the reaction mixture is diluted with a 10% aqueous citric acid solution and neutralized with an aqueous saturated sodium hydrogen carbonate solution. The solution is extracted with ethyl acetate. The ethyl acetate layer is washed, dried and concentrated in vacuo. The residue is separated with preparative thin-layer silica gel chromatography (solvent; ethyl acetate) to give 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-(4-hydroxypiperidin-1-yl)-2-(2-hydroxymethyl-1-pyrrolidinyl)pyrimidine as a colorless caramel 36mg.

IR (Nujol)cm<sup>-1</sup>: 3332, 1654, 1575, 1527, 1501, 1459

APCI-MS(m/z): 506(M+H)<sup>+</sup>

#### Example 322

(1) To a solution of 5-carboxy-2,4,6-trichloropyrimidine 10.0g in dimethylformamide 45ml is added a suspension of 3-chloro-4-methoxybenzylamine 4.82g and triethylamine 6.98ml in dimethylformamide 40ml over a period of 20 minutes on ice bath, and the mixture is stirred for 1 hour. The reaction mixture is diluted with a 10% aqueous citric acid solution and extracted with ethyl acetate. The organic layer is washed, dried and concentrated in vacuo to give 4-(3-chloro-4-methoxybenzylamino)-5-carboxy-2,6-dichloropyrimidine as a pale brown solid, 17.59g. mp150-151°C

(2) A mixture of 4-(3-chloro-4-methoxybenzylamino)-5-carboxy-2,6-dichloropyrimidine (prepared in the above (1)) 17.55g, sodium hydrogen carbonate 4.07g, methyl iodide 5.48ml and dimethylformamide 50ml is stirred overnight at room

temperature. The reaction mixture is diluted an aqueous saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer is washed, dried and concentrated in vacuo to give a pale yellow solid. The solid is suspended in a mixture of methylene chloride, isopropyl ether and hexane, and filtered. The precipitate is washed with a mixture of isopropyl ether and hexane to give 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-2,6-dichloropyrimidine as a colorless crystalline powder 8.64g. mp 118-119°C

(3) To a solution of 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-2,6-dichloropyrimidine (prepared in the above (2)) 1.01g in dimethylformamide 10ml are added 4-hydroxypiperidine 338mg and triethylamine 411mg at room temperature, and the mixture is stirred for 15 minutes. The reaction mixture is diluted with water and extracted with ethyl acetate. The organic layer is washed, dried and concentrated in vacuo to give a slightly yellow oil. The oil is separated with silica gel chromatography (solvent; chloroform: ethyl acetate = 8:1→5:1), and further separated with silica gel chromatography (solvent; hexane: ethyl acetate = 1:1) to give 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-chloro-2-(4-hydroxypiperidin-1-yl)pyrimidine as colorless crystals 540mg (mp 138-139°C) and 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-(4-hydroxypiperidin-1-yl)-2-chloropyrimidine as a colorless foam, 617mg.

(4) To a solution of 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-chloro-2-(4-hydroxypiperidin-1-yl)pyrimidine (prepared in the above (3)) 56mg in N,N-dimethylacetamide 0.5ml are added a solution of 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine 31mg in N,N-dimethylacetamide 0.5ml and triethylamine 27μl at room temperature, and the mixture is stirred at 80-90°C for 5 hours. The reaction mixture is diluted with an aqueous citric acid solution, made basic with an aqueous sodium

hydrogen carbonate solution and extracted with ethyl acetate. The organic layer is washed, dried and concentrated in vacuo to give 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-2-(4-hydroxypiperidin-1-yl)pyrimidine as a pale yellow powder, 66mg.

mp 191-194°C

IR (Nujol)cm<sup>-1</sup>: 3342, 3167, 1648, 1567, 1529, 1462, 1441

APCI-MS(m/z): 528(M+H)<sup>+</sup>

#### Example 323

(1) 4-(3-Chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-chloro-2-(4-methylpiperazin-1-yl)pyrimidine is obtained as a yellow crystalline powder by reacting 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-2,6-dichloropyrimidine and N-methylpiperazine in the same manner as Example 322 (3).

IR (Nujol)cm<sup>-1</sup>: 3314, 1659, 1585, 1539, 1241

APCI-MS(m/z): 440(M+H)<sup>+</sup>

(2) 4-(3-Chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-2-(4-methylpiperazin-1-yl)pyrimidine is obtained by reacting 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-chloro-2-(4-methylpiperazin-1-yl)pyrimidine (prepared in the above (1)) and 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine in the same manner as Example 463(4).

The above compound is made into its hydrochloride in the conventional manner.

IR (Nujol)cm<sup>-1</sup>: 3386, 1668, 1623, 1461, 1377

APCI-MS(m/z): 527(M+H)<sup>+</sup>

#### Example 324



To a solution of 6,7-dihydro-5-pyrrolo[3,4-b]pyridine 77mg in N,N-dimethylacetamide 2ml are added 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-(4-hydroxypiperidin-1-yl)-2-chloropyrimidine (prepared in Example 322 (3)) 105mg and triethylamine 75mg, and the mixture is stirred at room temperature for 1 hour, at 80-90°C for 3 hours and then at 100-110°C for 2 hours. The reaction mixture is diluted with water and extracted with ethyl acetate. The ethyl acetate layer is washed, dried and concentrated in vacuo to give a dark brown oil. The oil is separated with silica gel chromatography (solvent; chloroform: ethyl acetate = 1:1→ethyl acetate) to give 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-(4-hydroxypiperidin-1-yl)-2-(6,7-dihydro-5-pyrrolo[3,4-b]pyridin-6-yl)pyrimidine as a slightly brown solid, 76mg. mp 165-172°C (decomposition)

#### Example 325

(1) 4-(3-Chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-(4-hydroxypiperidin-1-yl)-2-(2-pyridylmethoxy)pyrimidine is obtained as a foam by reacting 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-(4-hydroxypiperidin-1-yl)-2-chloropyrimidine and 2-(hydroxymethyl)pyridine in the same manner as Example 324. IR (Neat+CHCl<sub>3</sub>)cm<sup>-1</sup>: 3344, 1663, 1582, 1537, 1501, 1440, 1410, 1345, 1260 APCI-MS(m/z): 514(M+H)<sup>+</sup>

#### Example 326

(1) To a solution of 4-(2-hydroxyethyl)phenol 9.50g in acetic acid 60ml is dropped bromine 3.54ml over a period of 10 minutes on a water bath, and the mixture is stirred for 15 minutes. The reaction mixture is diluted with water and extracted with ethyl acetate. The ethyl acetate layer is washed, dried and concentrated in vacuo. The

residue is dissolved in methanol 120ml and thereto is added potassium carbonate 25g. The mixture is stirred at room temperature for 5 hours. and then diluted with water and with ethyl acetate. The solution is acidified with concentrated sulfuric acid. The organic layer is extracted with ethyl acetate, washed, dried and concentrated in vacuo. The residue is crystallized from chloroform to give 2-bromo-4-(2-hydroxyethyl)phenol as a slightly brown crystalline powder 9.37g. mp 83-85°C

Furthermore, a mother liquid is concentrated in vacuo and separated with silica gel chromatography (solvent; chloroform: ethyl acetate = 10:1→5:1), to give 2-bromo-4-(2-hydroxyethyl)phenol as a colorless crystalline powder 2.72g. mp 85-86°C

(2) To a solution of 2-bromo-4-(2-hydroxyethyl)phenol (prepared in the above (1)) 11.79g in N,N-dimethylacetamide 155ml are added 28% sodium methoxide/methanol 9.43g and merryfield resin (chloro methylated styrene-divinylbenzene copolymer) 15.28g at room temperature, and the mixture is stirred for 18 hours at 80°C. After cooling the resin is filtered, washed and dried to give 2-bromo-4-(2-hydroxyethyl)phenoxymethyl resin 21.50g.

(3) A mixture of 4-(3-chloro-4-methoxybenzylamino)-5-carboxy-6-chloro-2-methylthiopyrimidine 10.50g and thionyl chloride 25ml is stirred for 20 minutes at 75°C. After reaction thionyl chloride is distilled off and the solvent is removed by azeotrope with methylene chloride to give 4-(3-chloro-4-methoxybenzylamino)-5-chloroformyl-6-chloro-2-methylthiopyrimidine.

(4) To a mixture of 2-bromo-4-(2-hydroxyethyl)phenoxymethyl resin (prepared in the above (2)) 8.84g and phenyldimethylamine (6.23ml) in methylene chloride 70ml is added a solution of a whole amount of 4-(3-chloro-4-methoxybenzylamino)-5-chloroformyl-6-chloro-2-methylthiopyrimidine (prepared in the above (3)) in methylene chloride 40ml at room temperature, and the mixture is stirred for 21 hours. After

filtration the resin is washed and dried to give 4-(3-chloro-4-methoxybenzylamino)-5-[2-(4-resin-methoxy-3-bromophenyl)ethoxycarbonyl]-6-chloro-2-methylthiopyrimidine 13.60g.

#### Examples 327-335

(1) 4-(3-Chloro-4-methoxybenzylamino)-5-[2-(4-resin-methoxy-3-bromophenyl)ethoxycarbonyl]-6-chloro-2-methylthiopyrimidine (prepared in Example 326(4)) and a corresponding starting compound are reacted in the same manner as Example 312(3), namely the resin combined with a compound is suspended in dimethylformamide and thereto are added triethylamine (3 mol) and R-H (an amine represented by the following Table 16)(3 mol), and the mixture is stirred for 16 hours at room temperature. The resin is filtered, washed with dimethylformamide, hydrous dimethylformamide(50%), water, methanol, tetrahydrofuran, isopropyl ether, respectively several times, and then dried in vacuo to give each compound listed in the following Table 16.

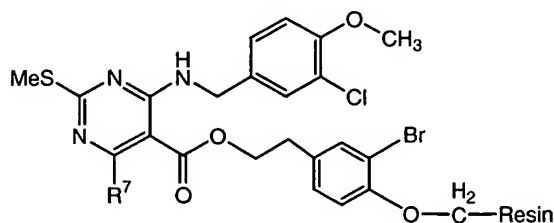
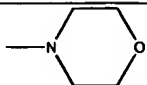

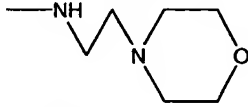
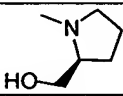
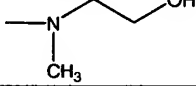


Table 16

Example No.	R <sup>7</sup>
327-1	
328-1	
329-1	

330-1	
331-1	
332-1	
333-1	$\text{—NMe}_2$
334-1	
335-1	

(2) Each resin prepared in the above (1) and a corresponding starting compound are reacted in the same manner as Example 321(4), namely the resin reacted is suspended in methylene chloride and swelled, and thereto are added a solution of m-chloroperbenzoic acid (1-2.5 mol) in methylene chloride and the mixture is stirred for 16 hours at room temperature. The resin is filtered, washed with methylene chloride, dimethylacetamide, methanol and isopropyl ether, respectively several times, and then dried in vacuo to give each compound listed in the following Table 17.

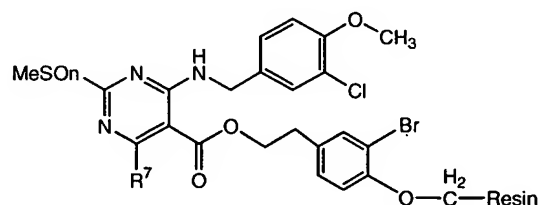
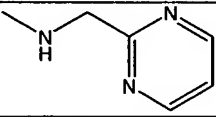
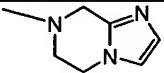


Table 17

Example No.	R <sup>7</sup>	n
327-2		1
328-2		2

329-2		2
330-2		2
331-2		2
332-2		1
333-2	$\text{—NMe}_2$	2
334-2		2
335-2		2

(3) Each resin prepared in the above (2) and a corresponding starting compound are reacted in the same manner as Example 321(5), namely the resin reacted is suspended in dimethylacetamide and thereto are added triethylamine (4 mol) and L-prolinol (4 mol), and the mixture is stirred for 9 hours at 75°C. After cooling to room temperature the resin is filtered, washed with dimethylacetamide and methanol, respectively several times to give each compound listed in the following Table 18.

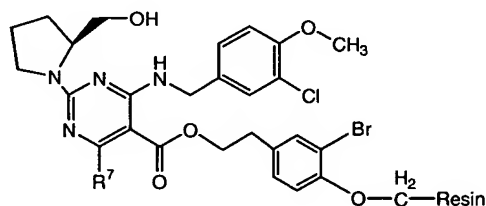


Table 18

Example No.	R <sup>7</sup>
327-3	
328-3	

329-3	
330-3	
331-3	
332-3	
333-3	$\text{—NMe}_2$
334-3	
335-3	

(4) Each resin prepared in the above (3) and a corresponding starting compound are reacted in the same manner as Example 321(6), namely the resin reacted is suspended in tetrahydrofuran and thereto is added sodium methoxide/methanol (10 mol). The mixture is stirred at 65°C for 2.5 hours. After cooling the reaction mixture is diluted with a 10% aqueous citric acid solution and neutralized with an aqueous saturated sodium hydrogen carbonate solution. The solution is extracted with ethyl acetate. The ethyl acetate layer is washed with an aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue is purified with silica gel chromatography, preparative thin-layer chromatography, etc. to give compounds listed in Table 19, Examples 332-4, 334-4 and 335-4.

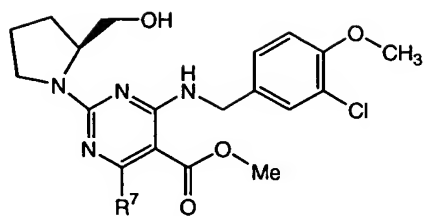
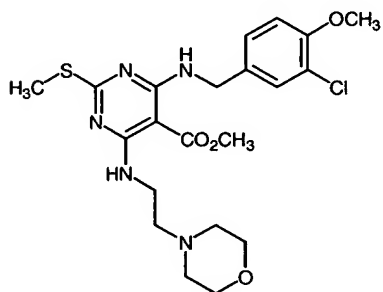


Table 19

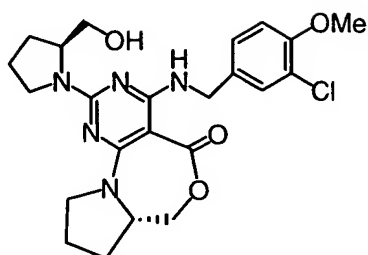
Example No.	R <sup>7</sup>	Physical property etc.
327-4		APCI-MS(m/z): 514(M+H) <sup>+</sup>
328-4		APCI-MS(m/z): 528(M+H) <sup>+</sup>
329-4		APCI-MS(m/z): 520(M+H) <sup>+</sup>
330-4		APCI-MS(m/z): 492(M+H) <sup>+</sup>
331-4		APCI-MS(m/z): 534(M+H) <sup>+</sup>
333-4	—NMe <sub>2</sub>	APCI-MS(m/z): 450(M+H) <sup>+</sup>

Example 332-4



APCI-MS(m/z): 482(M+H)<sup>+</sup>

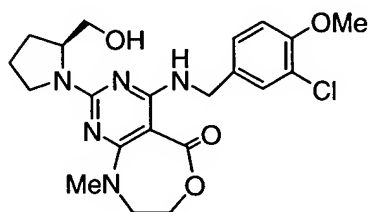
Example 334-4



Foam

APCI-MS(m/z): 474(M+H)<sup>+</sup>

Example 335-4



Foam

APCI-MS(m/z): 448(M+H)<sup>+</sup>

Examples 336 to 346

4-(3-Chloro-4-methoxybenzylamino)-5-[2-(4-resin-methoxy-3-bromophenyl)ethoxycarbonyl]-6-chloro-2-methylthiopyrimidine prepared in Example 326(4) and a corresponding starting compound (R<sup>1</sup>H) are reacted in the same manner as Example 327-335(1)-(4), to give compounds listed in the following Table 20 and compounds of Examples 340 and 341.



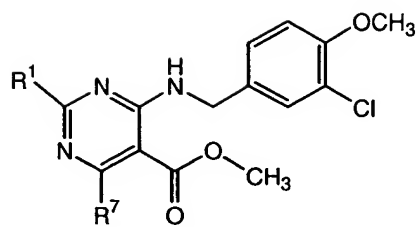
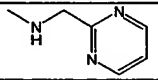
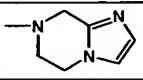
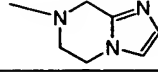
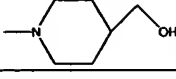
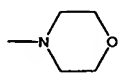
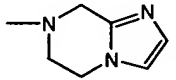
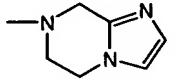
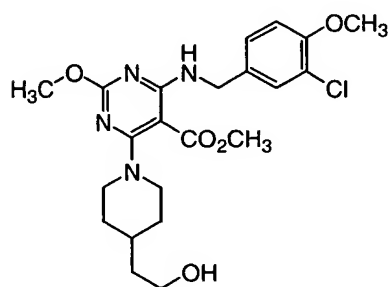


Table 20

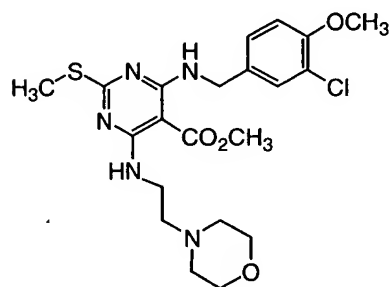
Example No.	R <sup>7</sup>	R <sup>1</sup>	Physical property etc.
336			mp: 184-186°C
337			APCI-MS(m/z): 542 (M+H) <sup>+</sup>
338			APCI-MS(m/z): 514(M+H) <sup>+</sup>
339	—NMe <sub>2</sub>		APCI-MS(m/z): 472(M+H) <sup>+</sup>

## Example 340



mp 111-114°C.

## Example 341

APCI-MS(m/z): 482(M+H)<sup>+</sup>

## Example 342

To a solution of 4-(3-chloro-4-methoxybenzylamino)-5-[2-(4-resin-methoxy-3-bromophenyl)ethoxycarbonyl]-6-chloro-2-methylthiopyrimidine (prepared in Example 326(4)) 1.20g in tetrahydrofuran 8 ml is gradually added a solution of 28% sodium methoxide/methanol 229mg in tetrahydrofuran 3ml at room temperature. The mixture is stirred for 2 hours. After filtration the resin is washed with tetrahydrofuran and dimethylformamide. The filtrate and washed solution is diluted with a 10% aqueous citric acid solution and neutralized with an aqueous saturated sodium hydrogen carbonate solution. The solution is extracted with ethyl acetate. The ethyl acetate layer is washed, dried and concentrated in vacuo to give 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-methoxy-2-methylthiopyrimidine as a colorless caramel, 293mg. mp 124-126°C

(2) A mixture of 4-(3-chloro-4-methoxybenzylamino)-5-methoxycarbonyl-6-methoxy-2-methylthiopyrimidine (prepared in the above (1)) 271mg, a 2.0M aqueous sodium hydroxide solution 3.53ml, water 2ml and dimethyl sulfoxide 6ml is stirred at 65°C for 14 hours. After cooling the reaction mixture is neutralized with a 10% aqueous citric acid solution and extracted with ethyl acetate. The ethyl acetate layer is washed, dried and concentrated in vacuo and the resulting powder is triturated with isopropyl ether to give 4-(3-chloro-4-methoxybenzylamino)-5-carboxy-6-methoxy-2-methylthiopyrimidine as a colorless crystalline powder, 210mg. mp 167-170°C

(3) To a mixture of 4-(3-chloro-4-methoxybenzylamino)-5-carboxy-6-methoxy-2-methylthiopyrimidine (prepared in the above (2)) 183mg, 2-aminomethylpyrimidine 70mg, 1-hydroxybenzotriazole hydrate 67mg and dimethylformamide 4ml is added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimido hydrochloride 114mg on an ice bath, and the mixture is stirred for 14 hours at room temperature. The reaction mixture is diluted with an aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The

ethyl acetate layer is washed, dried and concentrated in vacuo. The residue is separated with silica gel chromatography (solvent; chloroform: ethyl acetate = 20:1→10:1) to give 4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]-6-methoxy-2-methylthiopyrimidine as a colorless crystalline powder 208mg. mp 171-172°C

(4) 4-(3-Chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]-6-methoxy-2-methylthiopyrimidine (prepared in the above (3)) is treated in the same manner as Example 321(4) to give 4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]-6-methoxy-2-methylsulfinylpyrimidine as a colorless powder.

(5) 4-(3-Chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]-6-methoxy-2-methylsulfinylpyrimidine (prepared in the above (4)) and L-prolinol is treated in the same manner as Example 321(5) to give 4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]-6-methoxy-2-(2-hydroxymethyl-1-pyrrolodiny)pyrimidine as a colorless crystalline powder 88mg. mp 153-154°C

#### Example 343

(1) 4,6-Dichloro-5-carboxy-2-methylthiopyrimidine prepared in Example 320(1) and 2-bromo-4-(2-hydroxyethyl)phenol prepared in Example 326(1) are treated in the same manner as Example 326(3) and (4) to give 5-[2-(4-resin-methoxy-3-bromophenyl)ethoxycarbonyl]-4,6-chloro-2-methylthiopyrimidine.

(2) 5-[2-(4-Resin-methoxy-3-bromophenyl)ethoxycarbonyl]-4,6-chloro-2-methylthiopyrimidine prepared in the above (1) and 2-(3, 4-dimethoxyphenyl)ethylamine 254mg (0.892 mmol/g) are suspended in dimethylformamide 1ml, and thereto is added triethylamine 23mg. To the mixture is added a solution of 3,4-

dimethoxyphenethylamine 41mg in dimethylformamide 1ml. The mixture is stirred for 23 hours at room temperature. The reacted resin is filtered, washed with dimethylformamide, hydrous dimethylformamide, methanol, tetrahydrofuran, isopropyl ether, respectively several times, and then dried in vacuo to give 4-(2-(3,4-dimethoxyphenyl)ethylamino-5-[2-(4-resin-methoxy-3-bromophenyl)ethoxycarbonyl]-6-chloro-2-methylthiopyrimidine 279mg.

(3) 4-(2-(3,4-Dimethoxyphenyl)ethylamino-5-[2-(4-resin-methoxy-3-bromophenyl)ethoxycarbonyl]-6-chloro-2-methylthiopyrimidine (prepared in the above (2)) 237mg is suspended in dimethylformamide 2.5ml. Thereto is added triethylamine 81µl and 4-hydroxypiperidine 59mg and the mixture is stirred for 14 hours at room temperature. The reacted resin is filtered, washed with dimethylformamide, hydrous dimethylformamide, methanol and dichloromethane, respectively several times, and then dried to give 4-(2-(3,4-dimethoxyphenyl)ethylamino)-5-[2-(4-resin-methoxy-3-bromophenyl)ethoxycarbonyl]-6-(4-hydroxypiperidin-1-yl)-2-methylthiopyrimidine.

(4) 4-(2-(3,4-Dimethoxyphenyl)ethylamino)-5-[2-(4-resin-methoxy-3-bromophenyl)ethoxycarbonyl]-6-(4-hydroxypiperidine-1-yl)-2-methylthiopyrimidine prepared in the above (3) is suspended in dichloromethane 2.5ml. After swelling m-chloroperbenzoic acid 119mg is added thereto and the mixture is stirred for 9 hours at room temperature. The reacted resin is filtered, washed with dichloromethane, dimethylacetamide and methanol, respectively several times, and then dried to give 4-(2-(3,4-dimethoxyphenyl)ethylamino)-5-[2-(4-resin-methoxy-3-bromophenyl)ethoxycarbonyl]-6-(4-hydroxypiperidin-1-yl)-2-methylsulfinylpyrimidine.

(5) 4-(2-(3,4-Dimethoxyphenyl)ethylamino)-5-[2-(4-resin-methoxy-3-bromophenyl)ethoxycarbonyl]-6-(4-hydroxypiperidin-1-yl)-2-methylsulfinylpyrimidine prepare in the above (4) is suspended in dimethylacetamide 2.5ml, and thereto are

added triethylamine 108 $\mu$ l and L-prolinol 76 $\mu$ l. The mixture is stirred for 9 hours at 75°C. The reacted resin is filtered, washed with dimethylacetamide and tetrahydrofuran, respectively several times, and then dried to give 4-(2-(3,4-dimethoxyphenyl)ethylamino)-5-[2-(4-resin-methoxy-3-bromophenyl)ethoxycarbonyl]-6-(4-hydroxypiperidin-1-yl)-2-(2-hydroxymethyl-1-pyrrolidiny)pyrimidine.

(6) 4-(2-(3,4-Dimethoxyphenyl)ethylamino)-5-[2-(4-resin-methoxy-3-bromophenyl)ethoxycarbonyl]-6-(4-hydroxypiperidin-1-yl)-2-(2-hydroxymethyl-1-pyrrolidiny)pyrimidine prepared in the above (5) is suspended in tetrahydrofuran 2 ml, and thereto is added 28% sodium methoxide/methanol 370mg. The mixture is stirred at 55°C for 2.5 hours. After filtration the resin is washed with tetrahydrofuran. The filtrate is diluted with a 10% aqueous citric acid solution and made weakly alkaline with an aqueous saturated sodium hydrogen carbonate solution. The solution is extracted with methylene chloride. The combined organic layer is washed with an aqueous saturated sodium chloride solution, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue is separated and purified with silica gel chromatography (eluate; chloroform: ethyl acetate = 1:1 $\rightarrow$ ethyl acetate) to give 4-(2-(3,4-dimethoxyphenyl)ethylamino)-5-methoxycarbonyl-6-(4-hydroxypiperidin-1-yl)-2-(2-hydroxymethyl-1-pyrrolidiny)pyrimidine as a colorless foam, 20mg.

APCI-MS(m/z): 516(M+H)<sup>+</sup>

#### Example 344

(1) A mixture of dimethyl N-cyanodithioiminocarbonate 3.21g, L-prolinol 2.31g and chloroform 22ml is stirred at room temperature for a day. After reaction the mixture is separated with silica gel chromatography (solvent; hexane: ethyl acetate = 1:3 $\rightarrow$ ethyl acetate) to give a compound 1.65g. mp 44-48°C

(2) To a mixture of 1-mercaptacetic acid ethyl ester 1.06ml and triethylamine 9ml is added the compound (prepared in the above (1)) 1.46g at room temperature, and the mixture is stirred for a day. After reaction triethylamine is distilled off and the residue is separated with silica gel chromatography (solvent; hexane: ethyl acetate = 1:4) to give 4-amino-5-ethoxycarbonyl-2-(2-hydroxymethyl-1-pyrrolodiny)thiazole as a colorless viscous oil, 197mg.

IR (Neat) $\text{cm}^{-1}$ : 3441, 3324, 1656, 1613, 1545, 1509

APCI-MS( $m/z$ ): 272( $M+H$ )<sup>+</sup>

(3) To a mixture of 4-amino-5-ethoxycarbonyl-2-(2-hydroxymethyl-1-pyrrolodiny)thiazole (prepared in the above (2)) 177mg, 3-chloro-4-methoxybenzaldehyde 111mg, acetic acid 78mg and 1,2-dichloroethane 8ml is added sodium triacetoxymethylborohydride 415mg, and the mixture is stirred at room temperature for 6 hours. Further 3-chloro-2,5,4-methoxybenzaldehyde 111mg and sodium triacetoxymethylborohydride 415mg are added thereto, and the mixture is stirred at room temperature for 3 days. The reaction mixture is diluted with an aqueous sodium hydrogen carbonate solution and the organic layer is washed, dried and concentrated in vacuo. The residue is separated with reversed phase column chromatography and preparative thin-layer chromatography, and then triturated with ether to give 4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonyl-2-(2-hydroxymethyl-1-pyrrolodiny)thiazole as crystals, 171mg. mp 103.5-104.5°C

#### Example 345

(1) A solution of carbobenzoxychloride 7.87g in methylene chloride 50ml is dropped to a mixture of L-prolinol 4.9g in methylene chloride 50ml and sodium hydrogen carbonate 11.6g in water 50ml at 0°C under vigorously agitation. The mixture is stirred

for 1 hour at room temperature. The organic layer is separated, washed, dried and concentrated in vacuo to give N-carbobenzoxyl-L-prolinol 10.25g.

(2) To a mixture of N-carbobenzoxyl-L-prolinol (prepared in the above (1)) 5.26g, diisopropylamine 45ml and dimethylformamide 22ml is dropped methoxymethyl chloride 4.1g at 0°C, and the mixture is stirred for 3 days at room temperature. The reaction mixture is diluted with water and extracted with ethyl acetate. The organic layer is neutralized with 10% hydrochloric acid, washed, dried and concentrated in vacuo. The residue is separated with silica gel chromatography (solvent; hexane: ethyl acetate = 2:1) to N-carbobenzoxyl-2-methoxymethoxymethylpyrrolidine 3.944g.

(3) To a solution of N-carbobenzoxyl-2-methoxymethoxymethylpyrrolidine (prepared in the above (2)) 3.9g in methanol 80ml is added palladium-carbon 1g at argon atmosphere. Hydrogen gas is blown through the mixture and the mixture is stirred at room temperature for 3 hours. After reaction catalyst is removed by filtration and the filtrate is concentrated in vacuo to give 2-methoxymethoxymethylpyrrolidine 2.02g.

(4) A mixture of 2-methoxymethoxymethylpyrrolidine (prepared in the above (3)) 2g, cyanoisothiocyanate dimethylacetal 2.24g and chloroform 20ml is stirred at room temperature for 24 hours. The reaction mixture is concentrated in vacuo and the residue is separated with silica gel chromatography (solvent; hexane: ethyl acetate = 1:1) to give N-cyano-2-methoxymethoxymethylpyrrolidinethiocarboimide acid methyl ester 2.746g.

(5) To a mixture of 1-mercaptacetic acid 1g and trifluoroacetic acid 5ml is added triphenylmethanol 2.8g, and the mixture is stirred at room temperature for 1 hour. After reaction trifluoroacetic acid is distilled off and the residue is separated with silica gel



chromatography (solvent; chloroform) and triturated with hexane to give 1-(triphenylmethylthio)acetic acid 1.233g. mp 155-158°C

(6) A mixture of 1-(triphenylmethylthio)acetic acid (prepared in the above (5)) 1.218g, 2-aminomethylpyrimidine 517mg, 1-hydroxybenzotriazole hydrate 540mg, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride 768mg and dimethylformamide 15ml is stirred at room temperature overnight. The reaction mixture is diluted with ethyl acetate and an aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate. The organic layer is washed, dried and concentrated in vacuo. The residue is triturated with ether to give N-(2-pyrimidinylmethyl)-1-(triphenylmethylthio)acetamide 1.416g. mp 171-173°C

(7) To a mixture of N-(2-pyrimidinylmethyl)-1-(triphenylmethylthio)acetamide 990mg, trifluoroacetic acid 5ml and methylene chloride 5ml is dropped triethylsilane 1.35g at 0°C, and the mixture is stirred for 5 minutes. The reaction mixture is concentrated in vacuo and the residue is separated with silica gel chromatography (solvent; chloroform: methanol = 80:1→25:1) to give N-(2-pyrimidinylmethyl)-1-mercaptoacetamide 451mg.

(8) A mixture of a compound (prepared in the above (4)) 515mg, N-(2-pyrimidinylmethyl)-1-mercaptoacetamide (prepared in the above (7)) 427mg and triethylamine 6ml is stirred at room temperature for 20 hours. The reaction mixture is further stirred at 60-70°C for 5 hours. The mixture is concentrated in vacuo and the residue is separated with silica gel chromatography (solvent; chloroform: methanol = 80:1) to give 4-amino-5-[N-(2-pyrimidinylmethyl)amido]-2-(2-methoxymethoxymethyl-1-pyrrolidinyl)thiazole 457mg.

(9) To a mixture of 4-amino-5-[N-(2-pyrimidinylmethyl)amido]-2-(2-methoxymethoxymethyl-1-pyrrolidinyl)thiazole (prepared in the above (8)) 345mg, 3-

chloro-4-methoxybenzaldehyde 401mg, acetic acid 141mg and 1,2-dichloroethane 14ml is added sodium triacetoxyborohydride 798mg, and the mixture is stirred overnight at room temperature. The reaction mixture is diluted with water and extracted with ethyl acetate. The organic layer is washed, dried and concentrated in vacuo. The residue is separated with reverse phase column chromatography to give 4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)amido]-2-(2-methoxymethoxymethyl-1-pyrrolidinyl)thiazole 334mg.

(10) To a mixture of 4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)amido]-2-(2-methoxymethoxymethyl-1-pyrrolidinyl)thiazole (prepared in the above (9)) 334mg and methanol 4ml is added concentrated hydrochloric acid 2ml, and the mixture is stirred at room temperature for 2 hours. The reaction mixture is diluted with chloroform and an aqueous sodium hydrogen carbonate solution and extracted with chloroform. The organic layer is dried and concentrated in vacuo. The residue is separated with silica gel chromatography (solvent; chloroform: methanol = 50:1) to give 4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)amido]-2-(2-hydromethyl-1-pyrrolidinyl)thiazole 213mg.

IR (Neat)cm<sup>-1</sup>: 3316, 2929, 2871, 1603, 1563, 1543, 1503

FAB-MS(m/z): 489(M+H)<sup>+</sup>

#### Example 346

(1) 4-(3-Chloro-4-methoxybenzylamino)-5-[2-(4-resin-methoxy-3-bromophenyl)ethoxycarbonyl-6-(N-methyl-2-hydroxyethylamino)-2-methylsulfinylpyrimidine and 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine are treated in the same manner as Examples 468-476(3) to give 4-(3-chloro-4-methoxybenzylamino)-5-[2-

(4-resin-methoxy-3-bromophenyl)ethoxycarbonyl-6-(N-methyl-2-hydroxyethylamino)-2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)pyrimidine.

(2) 4-(3-Chloro-4-methoxybenzylamino)-5-[2-(4-resin-methoxy-3-bromophenyl)ethoxycarbonyl-6-(N-methyl-2-hydroxyethylamino)-2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)pyrimidine (prepared in the above (1)) is treated in the same manner as Example 327-335(4) to 4-(3-chloro-4-methoxybenzylamino)-2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-9-methyl-8,9-dihydro-7H-pyrido[4,5-e][1,4]oxazepin-5-one.

APCI-MS(m/z): 470(M+H)<sup>+</sup>

#### Example 347

(1) 2-Bromo-4-(2-hydroxyethyl)phenoxymethyl-resin (prepared in Example 326(2)) (1.27 mmol/g) 30.00g is suspended in anhydrous methylene chloride 25ml. While triethylamine 13.28g is added thereto and the mixture is stirred, acryloyl chloride 6.19ml is dropped thereto under ice cooling in argon atmosphere over a period of 15 minutes. The reaction mixture is stirred at room temperature for 14 hours. The reacted resin compound is filtered, washed with methylene chloride, dimethylformamide, hydrous dimethylformamide, methanol, tetrahydrofuran and isopropyl ether, respectively several times, and dried in vacuo to give 2-bromo-4-(2-acryloyloxyethyl)phenoxymethyl-resin 35.78g.

(2) 2-Bromo-4-(2-acryloyloxyethyl)phenoxymethyl-resin (prepared in the above (1)) 35.09g is suspended in a mixture of tetrahydrofuran 200ml, dimethyl sulfoxide 80ml and ethanol 40ml. To the suspension are added triethylamine 10.37ml and 4-methoxy-3-chlorobenzylamine hydrochloride 15.49g, and the mixture is stirred at 60°C for 22 hours. The reacted resin compound is filtered, washed with tetrahydrofuran,

dimethylformamide, hydrous dimethylformamide, methanol and isopropyl ether, respectively several times, and dried in vacuo to give 2-bromo-4-(2-(3-(4-methoxy-3-chlorobenzylamino)propionyloxy)ethyl)phenoxymethyl-resin 38.93g.

(3) A mixture of 4,6-dichloro-5-carboxy-2-methylthiopyrimidine (prepared in Example 320(1)) 5.00g, N,N-dimethylacetamide 50ml, tetrahydrofuran 20ml and sodium hydride (60%) 1.673g is stirred for 20 minutes on an ice bath. Methanol 5ml is dropped thereto over a period of 30 minutes and the mixture is stirred for 15 minutes. The reaction mixture is diluted with a 10% aqueous citric solution and extracted with ethyl acetate. The organic layer is washed, dried and concentrated in vacuo. The resulting solid is triturated with hexane in ice to give 4-chloro-5-carboxy-6-methoxy-2-methylthiopyrimidine as a slightly brown crystalline powder, 4.61g. mp 179-181°C

(4) A mixture of 4-chloro-5-carboxy-6-methoxy-2-methylthiopyrimidine (prepared in the above (3)) 2.00g and thionyl chloride 5ml is stirred at 40°C for 15 minutes. Thionyl chloride, etc. is distilled off and the solvent is removed with azeotrope with methylene chloride to give 4-chloro-5-chloroformyl-6-methoxy-2-methylthiopyrimidine.

(5) To a mixture of whole amount of 4-chloro-5-chloroformyl-6-methoxy-2-methylthiopyrimidine (prepared in the above (4)) and methylene chloride 10ml is dropped a mixture of 2-aminomethylpyrimidine 930mg, triethylamine 2.38ml and methylene chloride 10ml over a period of 5 minutes on an ice bath, and the mixture is stirred for 20 minutes. The mixture is further stirred at room temperature for 40 minutes. The reaction mixture is diluted with water and the water layer is extracted with methylene chloride. The organic layer is dried and concentrated in vacuo. The residue is separated with silica gel chromatography (solvent; chloroform: ethyl acetate = 1:1) and recrystallized from a mixture of methylene chloride, ethyl acetate and isopropyl

ether to give 4-chloro-5-[N-(2-pyrimidinylmethyl)carbamoyl]-6-methoxy-2-methylthiopyrimidine as a colorless crystalline powder, 1.56g. mp 176-177°C

(6) 2-Bromo-4-(2-(3-(4-methoxy-3-chlorobenzylamino)propionyloxy)ethyl)phenoxymethyl-resin (prepared in the above (2)) 400mg is suspended in N,N-dimethylacetamide 3.5ml. To the suspension are added triethylamine 107µl and 4-chloro-5-[N-(2-pyrimidinylmethylcarbamoyl)-6-methoxy-2-methylthiopyrimidine (prepared in the above (5)) 249mg, and the mixture is stirred at 70°C for 17 hours. The reacted resin compound is filtered, washed with N,N-dimethylformamide, hydrous N,N-dimethylformamide, methanol, tetrahydrofuran and methylene chloride, respectively several times, and dried in vacuo to give 4-[N-(4-methoxy-3-chlorobenzyl)-N-[2-(4-resin-methoxy-3-bromophenethyloxycarbonyl)ethyl]amino]-5-[N-(2-pyrimidinylmethyl)carbamoyl]-6-methoxy-2-methylthiopyrimidine.

(7) The resin compound (prepared in the above (6)) is suspended in methylene chloride 2.5ml. To the suspension is added a solution of m-chloroperbenzoic acid 104mg in methylene chloride 1ml, and the mixture is stirred at room temperature for 16 hours. The reacted resin compound is filtered, washed with hydrous N,N-dimethylformamide, methanol, methylene chloride and N,N-dimethylacetamide, respectively several times, to give 4-[N-(4-methoxy-3-chlorobenzyl)-N-[2-(4-resin-methoxy-3-bromophenethyloxycarbonyl)ethyl]amino]-5-[N-(2-pyrimidinylmethyl)carbamoyl]-6-methoxy-2-methylsulfinylpyrimidine.

(8) The resin compound prepared in the above (7) is suspended in N,N-dimethylacetamide 2.5ml. To the suspension are added triethylamine 160µl and L-prolinol 116mg and then the mixture is stirred at 75°C for 14 hours. The reacted resin compound is filtered, washed with N,N-dimethylformamide, hydrous N,N-

dimethylformamide, methanol, tetrahydrofuran and a mixture of tert-butanol and tetrahydrofuran (1:9), respectively several times, to give 4-[N-(4-methoxy-3-chlorobenzyl)-N-[2-(4-resin-methoxy-3-bromophenethyloxycarbonyl)ethyl]amino]-5-[N-(2-pyrimidinylmethyl)carbamoyl]-6-methoxy-2-(2-hydroxymethyl-1-pyrrolidinyl)pyrimidine.

(9) The resin compound (prepared in the above (8)) is suspended in a mixture of tert-butanol and tetrahydrofuran(1:9). To the suspension is added tert- potassium butoxide 214mg under ice cooling. The mixture is stirred for 20 minutes. A 10% aqueous citric acid solution 2ml is added thereto and the resin is filtered, washed with tetrahydrofuran. The washed solution is made basic with an aqueous saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The combined organic layer is washed with an aqueous sodium chloride solution, dried over magnesium sulfate and concentrated in vacuo. The residue is separated and purified with preparative thin-layer silica gel chromatography (eluent; chloroform: ethyl acetate: methanol = 20:20:1) and recrystallized from a mixture of ethanol and isopropyl ether to give 4-(4-methoxy-3-chlorobenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]-6-methoxy-2-(2-hydroxymethyl-1-pyrrolidinyl)pyrimidine as a colorless crystalline powder, 28mg. mp 153-154°C

#### Examples 348-354

(1) The following compounds are prepared in the same manner in Example 347(3) and (4).

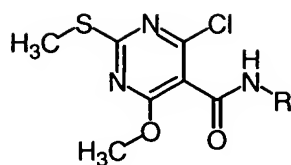


Table 21

	R	mp
348-1		120 - 122°C
349-1		133 - 134°C
350-1		195 - 197°C
351-1		155 - 156°C
352-1		155 - 158°C
353-1		193 - 195°C
354-1		109 - 112°C

(2) The following compounds are prepared starting from the compounds prepared in the above (1) in the same manner as Example 347(6).

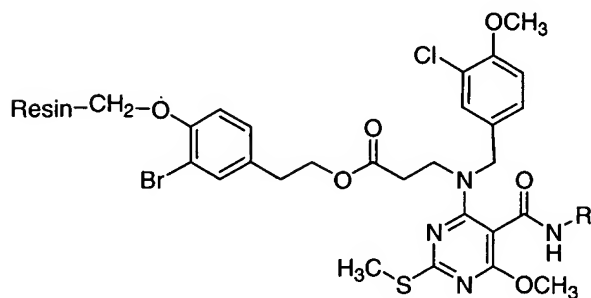


Table 22

R
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348-2	
349-2	
350-2	
351-2	
352-2	
353-2	
354-2	

#### Examples 355-394

The compounds listed in the following Tables 23-30 are prepared starting from the compounds prepared in the above (2) and Example 347 (5) in the same manner as Example 347(6)-(8).

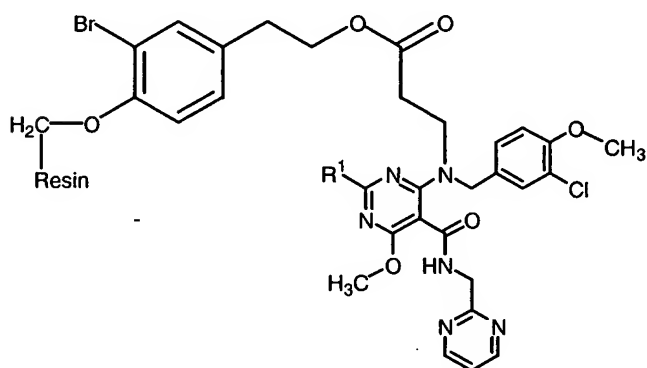
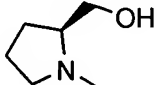
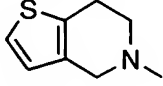
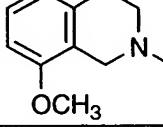
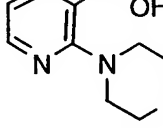
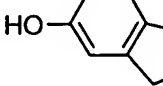


Table 23

Example No.	R <sup>1</sup>
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355	
356	
357	
358	
359	

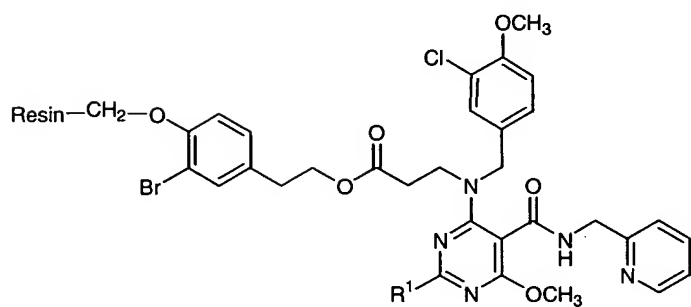
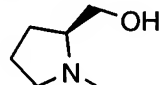
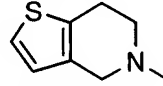
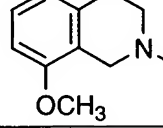
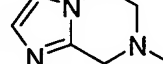
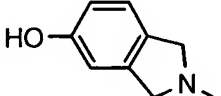


Table 24

Example No.	R <sup>1</sup>
360	
361	
362	
363	

364	
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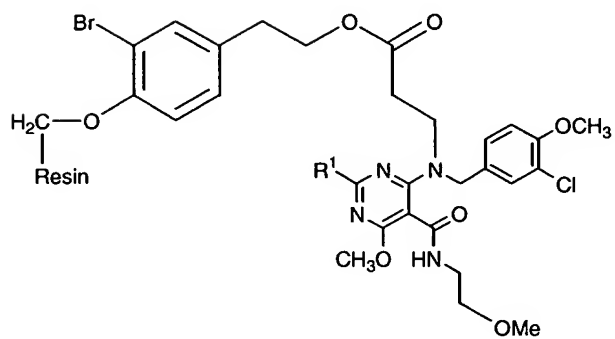
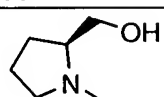
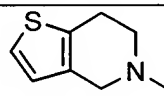
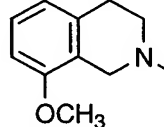
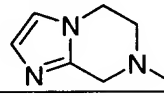
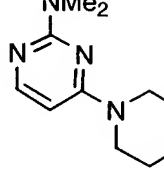


Table 25

Example No.	R <sup>1</sup>
365	
366	
367	
368	
369	

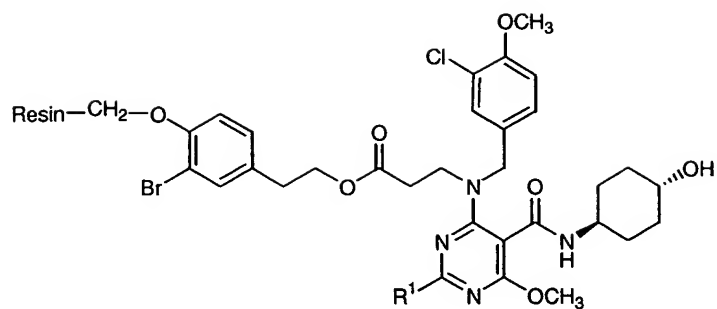


Table 26

Example No.	R <sup>1</sup>
370	
371	
372	
373	
374	

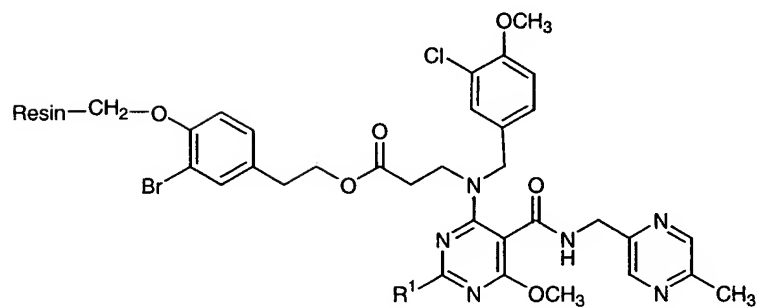
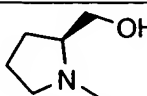
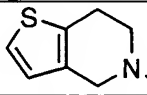
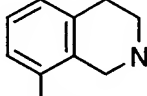
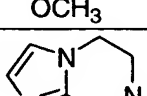
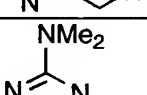


Table 27

Example No.	R <sup>1</sup>
375	
376	
377	
378	
379	

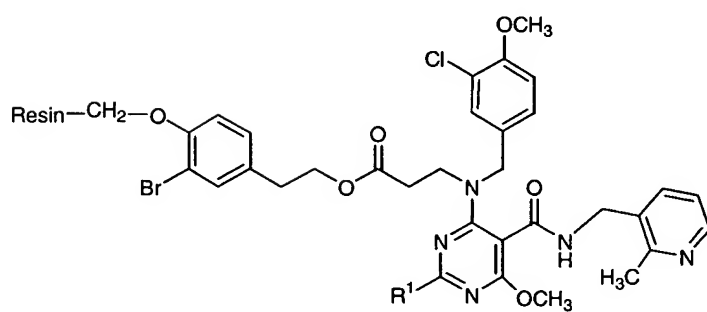
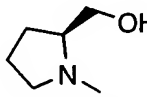
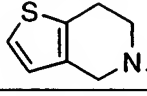
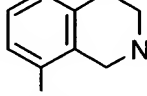
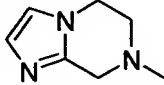
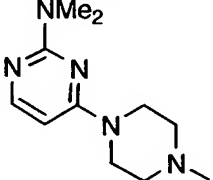


Table 28

Example No.	R <sup>1</sup>
380	
381	
382	

383	
384	

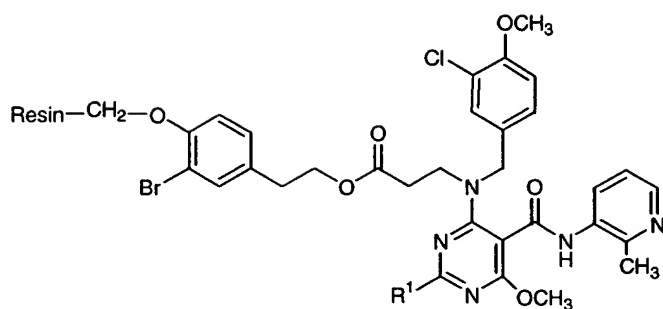
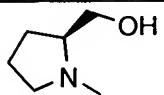
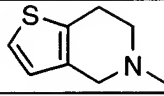
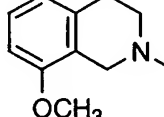
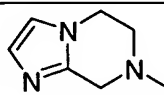
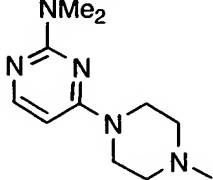


Table 29

Example No.	R <sup>1</sup>
385	
386	
387	
388	
389	

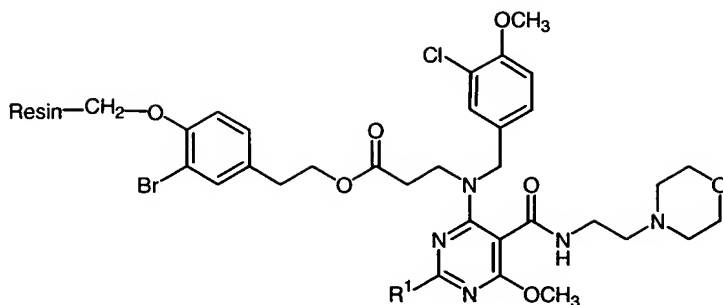


Table 30

Example No.	R <sup>1</sup>
390	
391	
392	
393	
394	

#### Examples 395-432

The compounds listed in the following Tables 31-39 are prepared by removing the resin from the compounds prepared in Example 347 (5) and Examples 355-395 in the same manner as Example 347(9).

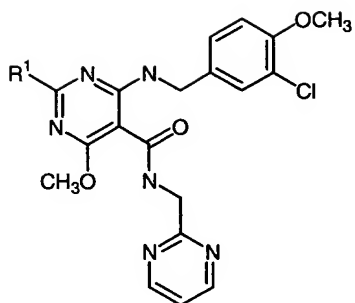


Table 31

Example No.	R <sup>1</sup>	Physical property etc.
395		mp: 153-154°C APCI-MS(m/z): 514 (M+H) <sup>+</sup>
396		mp: 152-155°C APCI-MS(m/z): 552 (M+H) <sup>+</sup>
397		mp: 169-172°C APCI-MS(m/z): 576 (M+H) <sup>+</sup>
398		Foam APCI-MS(m/z): 606 (M+H) <sup>+</sup>

Table 32

Example No.	Product	Physical property etc.
399		mp: 186-188°C APCI-MS(m/z): 456 (M+H) <sup>+</sup>

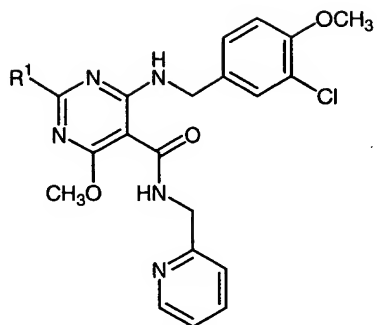


Table 33

Example No.	R <sup>1</sup>	Physical property etc.
400		Foam APCI-MS(m/z): 513 (M+H) <sup>+</sup>
401		mp: 153-155°C APCI-MS(m/z): 551 (M+H) <sup>+</sup>
402		mp: 137-139°C APCI-MS(m/z): 575 (M+H) <sup>+</sup>
403	A mixture of and	mp: 198-201°C APCI-MS(m/z): 547 (M+H) <sup>+</sup>

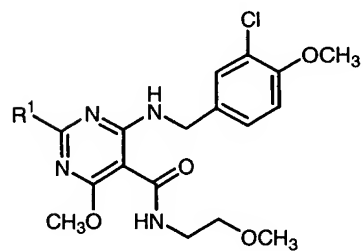
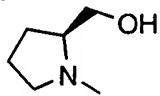
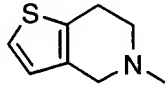

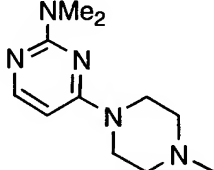




Table 34

Example No.	R <sup>1</sup>	Physical property etc.
404		Oil APCI-MS(m/z): 480 (M+H) <sup>+</sup>
405		Oil APCI-MS(m/z): 518 (M+H) <sup>+</sup>
406		mp: 93-96°C APCI-MS(m/z): 542 (M+H) <sup>+</sup>
407	HO—	mp: 216-218°C APCI-MS(m/z): 397 (M+H) <sup>+</sup>
408		mp: 71-73°C APCI-MS(m/z): 586 (M+H) <sup>+</sup>

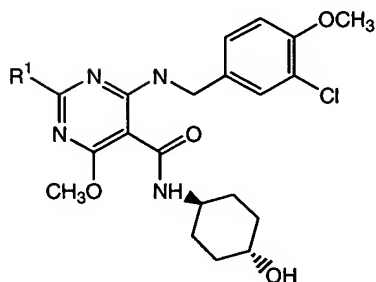
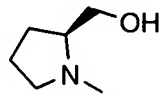
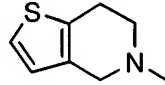
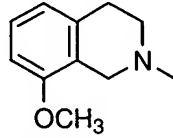
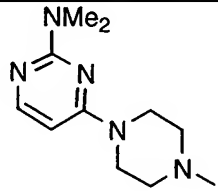


Table 35

Example No.	R <sup>1</sup>	Physical property etc.
409		Foam APCI-MS(m/z): 520 (M+H) <sup>+</sup>
410		Oil APCI-MS(m/z): 558 (M+H) <sup>+</sup>
411		Foam APCI-MS(m/z): 582 (M+H) <sup>+</sup>
412	nBuO—	Oil

		APCI-MS(m/z): 493 (M+H) <sup>+</sup>
413		Oil APCI-MS(m/z): 626 (M+H) <sup>+</sup>
414	HO—	mp 216-218°C APCI-MS(m/z): 437 (M+H) <sup>+</sup>

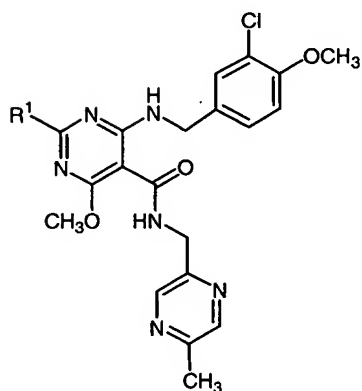
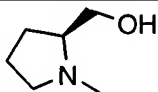
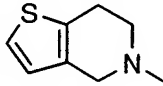
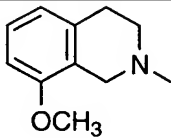
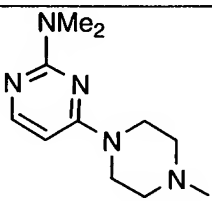


Table 36

Example No.	R <sup>1</sup>	Physical property etc.
415		Foam APCI-MS(m/z): 528(M+H) <sup>+</sup>
416		mp 140-142°C APCI-MS(m/z): 566(M+H) <sup>+</sup>
417		mp 163-165°C APCI-MS(m/z): 590(M+H) <sup>+</sup>
418	<i>n</i> BuO—	mp 98-101°C APCI-MS(/z): 501(M+H) <sup>+</sup>
419		mp 193-194°C APCI-MS(m/z): 634(M+H) <sup>+</sup>

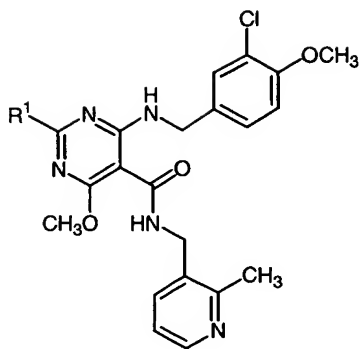


Table 37

Example No.	R <sup>1</sup>	Physical property etc.
420		Foam APCI-MS(m/z): 527 (M+H) <sup>+</sup>
421		mp 172-173°C APCI-MS(m/z): 565 (M+H) <sup>+</sup>
422		mp 86-88°C APCI-MS(m/z): 589 (M+H) <sup>+</sup>
423	CH <sub>3</sub> S—	mp 160-162°C APCI-MS(m/z): 474 (M+H) <sup>+</sup>
424		mp 182-184°C APCI-MS(m/z): 633 (M+H) <sup>+</sup>

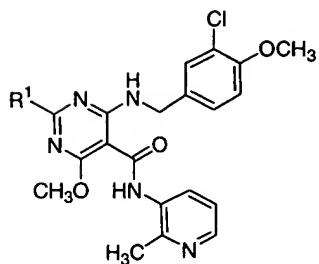
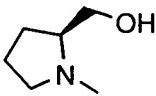
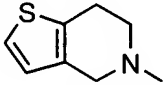
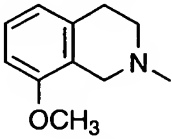
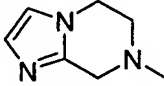
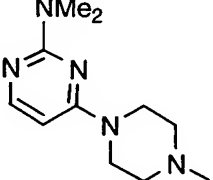


Table 38

Example No.	R <sup>1</sup>	Physical property etc.
425		Foam APCI-MS(m/z): 513 (M+H) <sup>+</sup>
426		Foam APCI-MS(m/z): 551 (M+H) <sup>+</sup>
427		APCI-MS(m/z): 575 (M+H) <sup>+</sup> mp 187-192°C
428		Foam APCI-MS(m/z): 535 (M+H) <sup>+</sup>
429		Foam APCI-MS(m/z): 619 (M+H) <sup>+</sup>

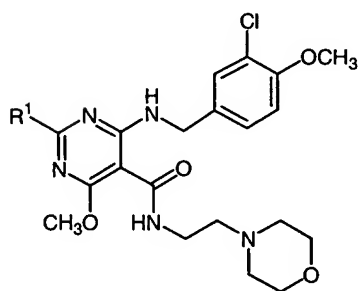
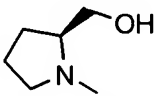
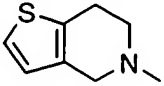
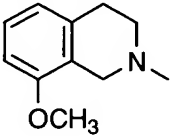


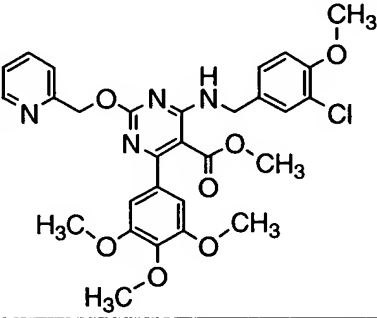
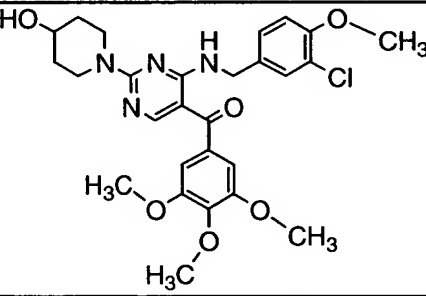
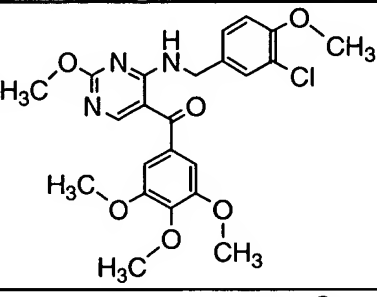
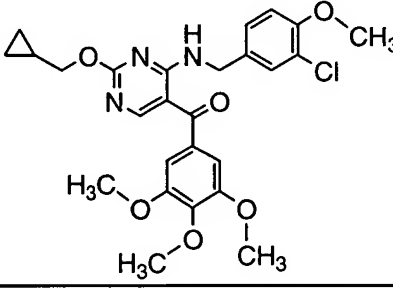
Table 39

Example No.	R <sup>1</sup>	Physical property etc.
430		Oil APCI-MS(m/z): 535 (M+H) <sup>+</sup>
431		Oil APCI-MS(m/z): 573 (M+H) <sup>+</sup>
432		Oil APCI-MS(m/z): 597 (M+H) <sup>+</sup>

Examples 433-482

The compounds listed in the following Table 15 are prepared as mentioned above.

Table 15-1

Example No.	Structure	Physical property etc.
433		mp 158-162°C
434		mp 132-133°C
435		mp 136-138°C
436		mp 98-100°C

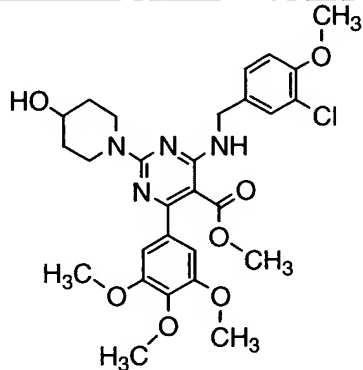
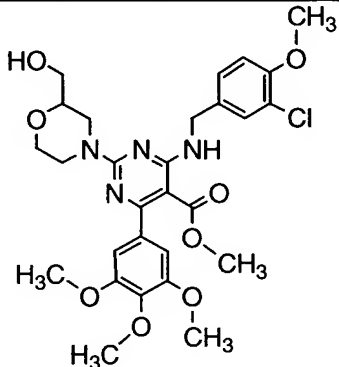
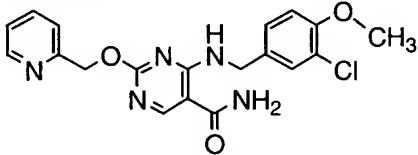
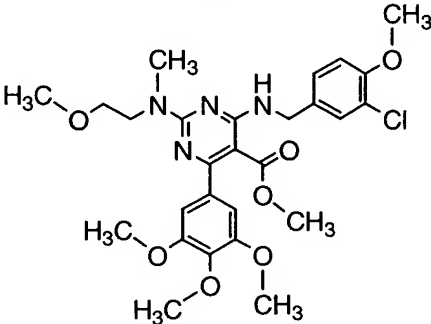
437		mp 169-171°C
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Table 15-2

Example No.	Structure	Physical property etc.
438		Foam MS(m/z): 589(M+H) <sup>+</sup>
439		mp 208-209°C
440		Foam MS(m/z): 561(M+H) <sup>+</sup>

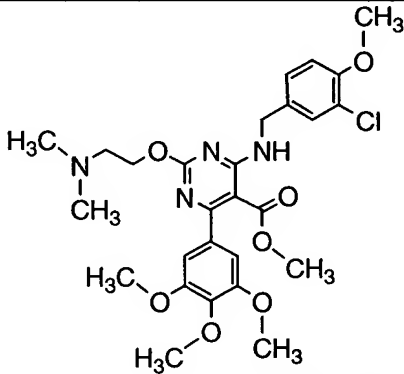
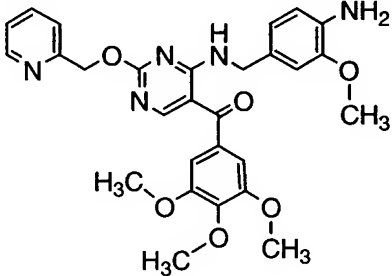
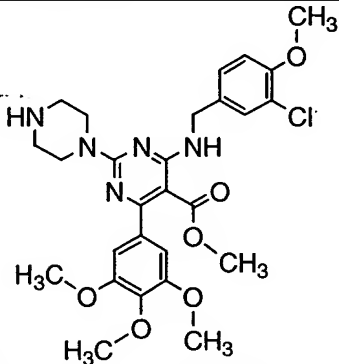
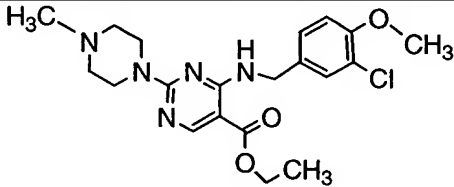
441		Foam MS(m/z): 561(M+H) <sup>+</sup>
442		mp 146-148°C

Table 15-3

Example No.	Structure	Physical property etc.
443		mp 153-155°C
444		mp 136.5-137.5°C

445		mp 112.5-113°C
446		mp 42-45°C
447		D.c. 90-130°C
448		Amorphous MS(m/z): 595(M+H) <sup>+</sup>

Table 15-4

Example No.	Structure	Physical property etc.
449		mp 139-140°C



450		mp 142-145°C
451		mp 149-150°C
452		D.c. 86-90°C
453		Powder MS(m/z): 506(M+H) <sup>+</sup>
454		Oil MS(m/z): 527(M+H) <sup>+</sup>

Table 15-5

Example No.	Structure	Physical property etc.
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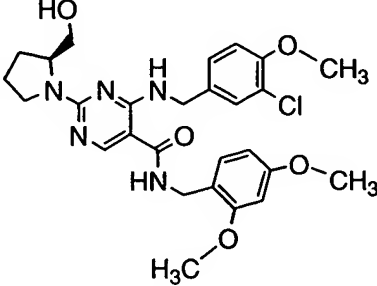
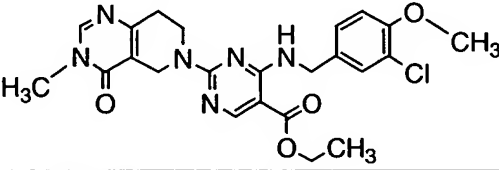
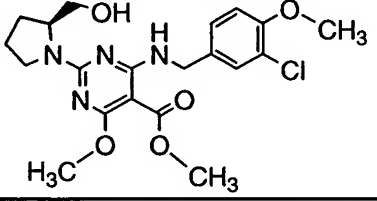
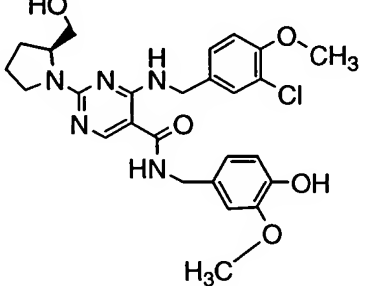
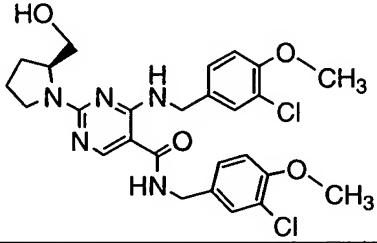
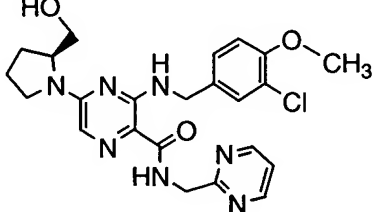
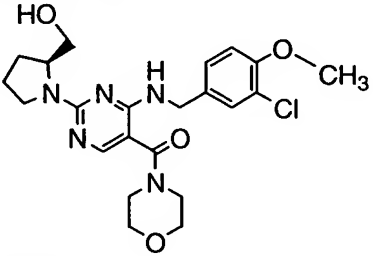
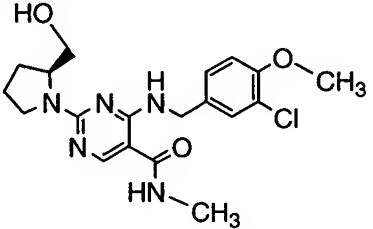
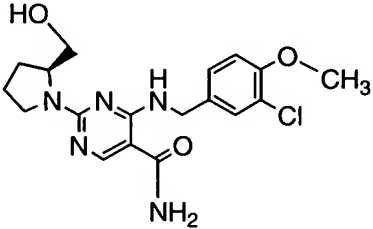
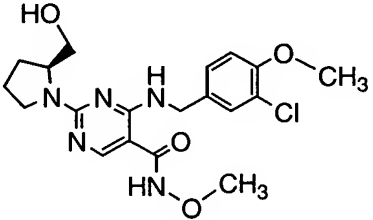
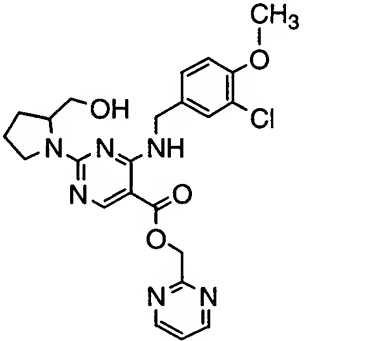
455		Foam MS(m/z): 542(M+H) <sup>+</sup>
456		mp 185-188°C
457		Foam MS(m/z): 437(M+H) <sup>+</sup>
458		Powder MS(m/z): 528(M+H) <sup>+</sup>
459		mp 158-160°C
460		Hydrochloride Powder MS(m/z): 484(M+H) <sup>+</sup>

Table 15-6

Example No.	Structure	Physical property etc.
461		Powder MS(m/z): 462(M+H) <sup>+</sup>
462		mp 191-193°C
463		mp 152.5-154.5°C
464		mp 155-157°C
465		mp 146-147°C

466		MS(m/z): 528(M+H) <sup>+</sup> mp 97°C
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Table 15-7

Example No.	Structure	Physical property etc.
467		Foam MS(m/z): 506(M+H) <sup>+</sup>
468		Foam MS(m/z): 548(M+H) <sup>+</sup>
469		mp 214-215°C
470		Foam MS(m/z): 544(M+H) <sup>+</sup>

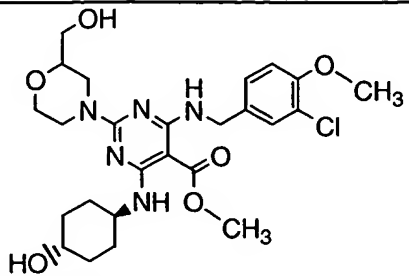
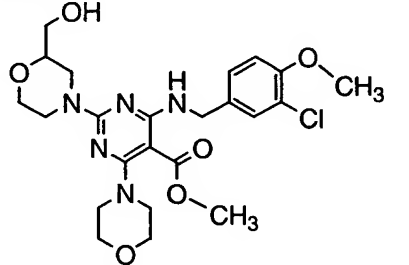
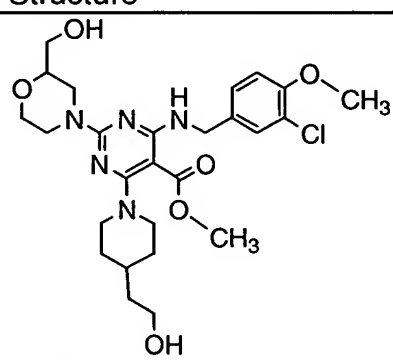
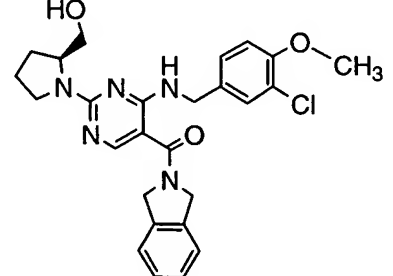
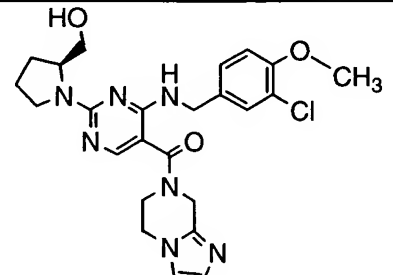
471		mp 176-182°C
472		Foam MS(m/z): 508(M+H) <sup>+</sup>

Table 15-8

Example No.	Structure	Physical property etc.
473		Foam MS(m/z): 548(M+H) <sup>+</sup>
474		Powder MS(m/z): 494(M+H) <sup>+</sup>
475		Powder MS(m/z): 498(M+H) <sup>+</sup>

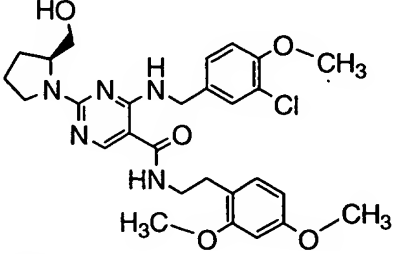
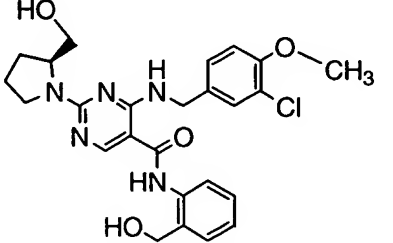
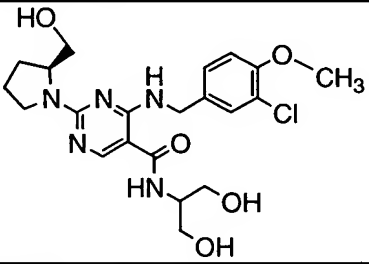
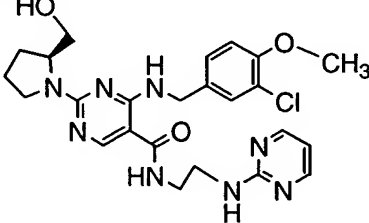
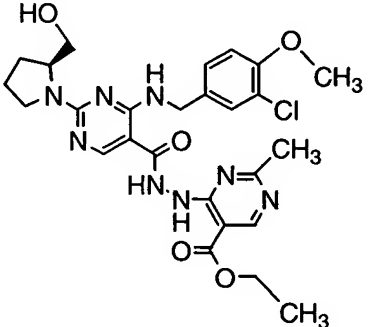
476		Powder MS(m/z): 556(M+H) <sup>+</sup>
477		Powder MS(m/z): 498(M+H) <sup>+</sup>

Table 15-9

Example No.	Structure	Physical property etc.
478		mp 184-185°C
479		mp 146-148°C
480		mp 208-209°C

481		mp 123-126°C
482		Powder MS(m/z): 486(M+H) <sup>+</sup>

### Reference example 1

(1) A solution of 2-cyanopyrimidine 80g in ethanol 400ml is put in a SL autoclave, and therein are 10% palladium-carbon 48g in ethanol and 15% ammonia/ethanol (ammonia 224g, 1.6L). After the atmosphere is three times substituted with 3 hydrogen pressure, the reaction is carried out at 7 hydrogen pressure for 5 hours. The mixture is filtered with precoated active carbon 40g and washed with ethanol. The solvent is removed under atmospheric pressure. To the residue is added ethanol and then gradually added maleic acid 97.2g and the mixture is stirred for 1 hour. To the mixture is dropped ethyl acetate 800ml over about a period of about 20 minutes. The mixture is gradually cooled to 30°C, and is stirred for 30 minutes under ice cooling. The resulting crystals are collected by filtration, washed with a mixture of ethanol and ethyl acetate (1:2) 160ml to give 2-aminomethylpyrimidine maleate 114.6g (yield: 67%).

(2) 2-Aminomethylpyrimidine maleate 70g and ethanol 280ml are put in a 4 neck-flask (2L). To the suspension is dropped a solution of hydrogen chloride in ethanol (previously prepared) 69.6g over a period of 10 minutes, and the mixture is stirred at

70°C for 2 hours. After reaction ethyl acetate 560ml is dropped thereto at 60°C and the mixture is gradually cooled to 30°C and stirred for 30 minutes under ice cooling. The resulting crystals are collected by filtration, washed with a cold mixture of ethanol and ethyl acetate (1:2) 140ml and dried to give 2-aminomethylpyrimidine hydrochloride as powder-like crystals 43.1g. mp 207-210 (decomposition)

#### Reference Example 2

Zinc chloride (136.3g, 1.0mol) and sodium borohydride (75.6g, 2.0mol) are added to chilled tetrahydrofuran (1035ml) under nitrogen atmosphere. After stirring for about 2 hours below 15°C, trimethylsilyl chloride (217.2g, 2.0mol) is added to the mixture and stirred for about 10 minutes. L-Proline (115.1g, 1.0mol) is gradually added to the mixture and stirred at 20°C for about 24 hours. After completion of the reaction, methanol (575ml) and a solution of sodium hydroxide (120.0g) in water (480ml) are added to the reaction mixture below 15°C and stirred for about an hour. The slurry is charged on centrifuge coated with celite (23g) and the separated insoluble matter is washed with tetrahydrofuran (230ml). The filtrate and washings are combined and concentrated under atmospheric pressure to remove organic solvents. The resultant aqueous solution is stirred at 95-100°C for about 2 hours. After cooling, a solution of sodium hydroxide (120.0g) in water (480ml) is added to the mixture and extracted with chloroform (3 x 575ml). The extract is dried over anhydrous potassium carbonate (57.5g). After removal of the drying agent by filtration and washed with chloroform (115ml), the filtrate and washings are combined and concentrated under atmospheric pressure. The resultant liquid is distilled under reduced pressure to produce L-prolinol (69.4g, 69%). bp 74-76°C/270Pa



## INDUSTRIAL APPLICABILITY

The compound (I) of the present invention and its pharmacologically acceptable salt have excellent specific PDE V inhibitory activity and therefore, are effective for treating various diseases due to functional disorders on cGMP-signaling, such as chronic or acute heart failure, myocardial infarction, erectile dysfunction, hypertension, pulmonary hypertension, diabetic gastroparesis, angina pectoris, female sexual dysfunction, prostatic hyperplasia, asthma, diarrhea, constipation, achalasia, etc.

The compound (I) of the present invention and its pharmacologically acceptable salt have excellent characteristic properties as they hardly show side effects including toxicity, exhibit selectively the desired effect and are safe as a medicine.